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Xie et al.

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(54) **HTRPV1 CHEMICAL AGENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 44 days.

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(65) **Prior Publication Data**

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Related U.S. Application Data

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(51) **Int. Cl.**

C07C 275/30 (2006.01)

C07C 275/34 (2006.01)

C07C 275/40 (2006.01)

C07C 275/42 (2006.01)

C07D 295/135 (2006.01)

C07C 275/32 (2006.01)

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(52) **U.S. Cl.**

CPC **C07C 275/30** (2013.01); **C07C 275/32** (2013.01); **C07C 275/34** (2013.01); **C07C 275/40** (2013.01); **C07C 275/42** (2013.01); **C07D 295/135** (2013.01)

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(58) **Field of Classification Search**

CPC **C07C 275/30**
See application file for complete search history.

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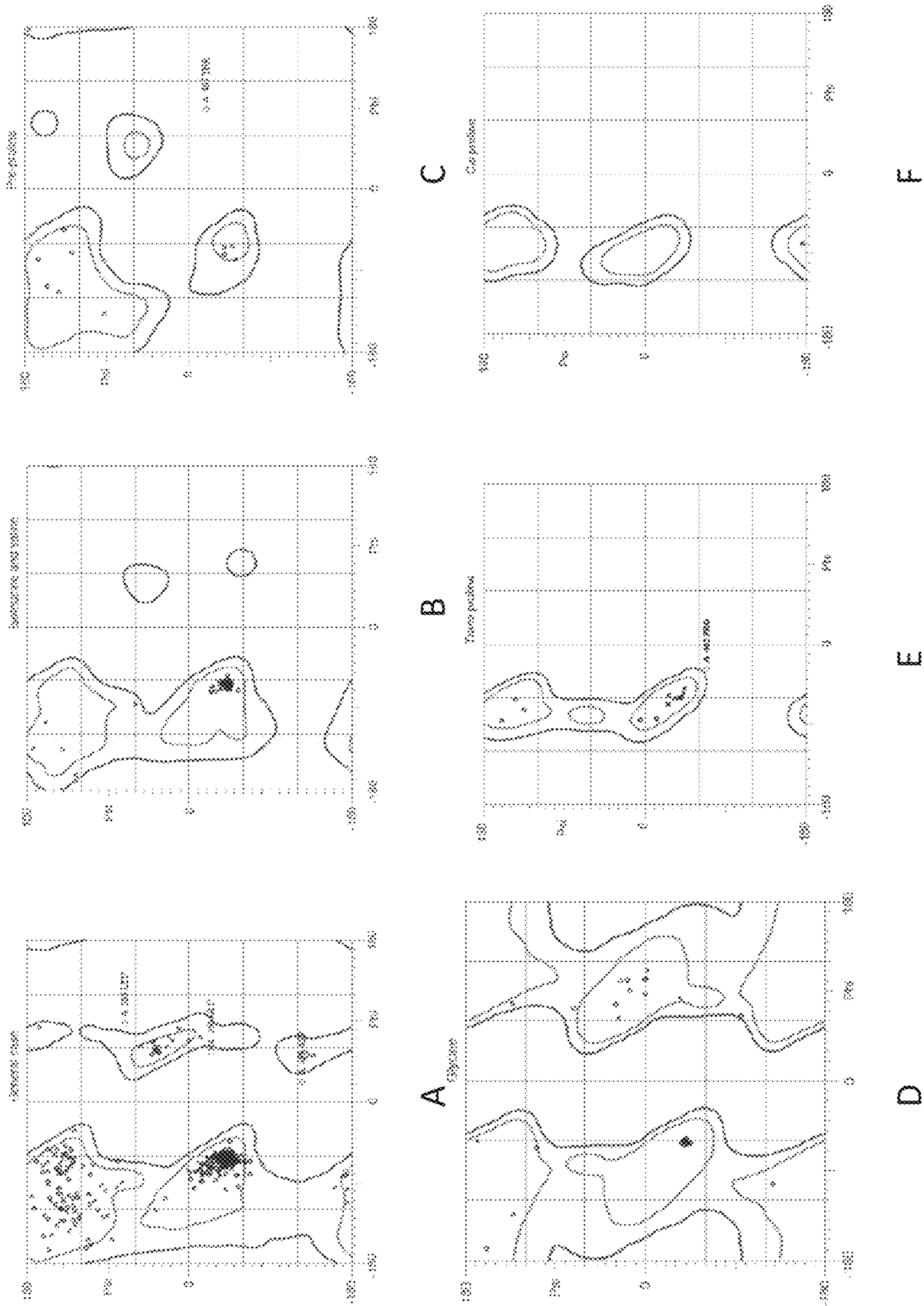
(57) **ABSTRACT**

Novel diphenylurea and benzylbenzenesulfonamide compounds are disclosed along with methods of inhibiting the activity of TRPV1 and methods of treating pain associated with transient receptor potential vanilloid type 1 (TRPV1) using such compounds.

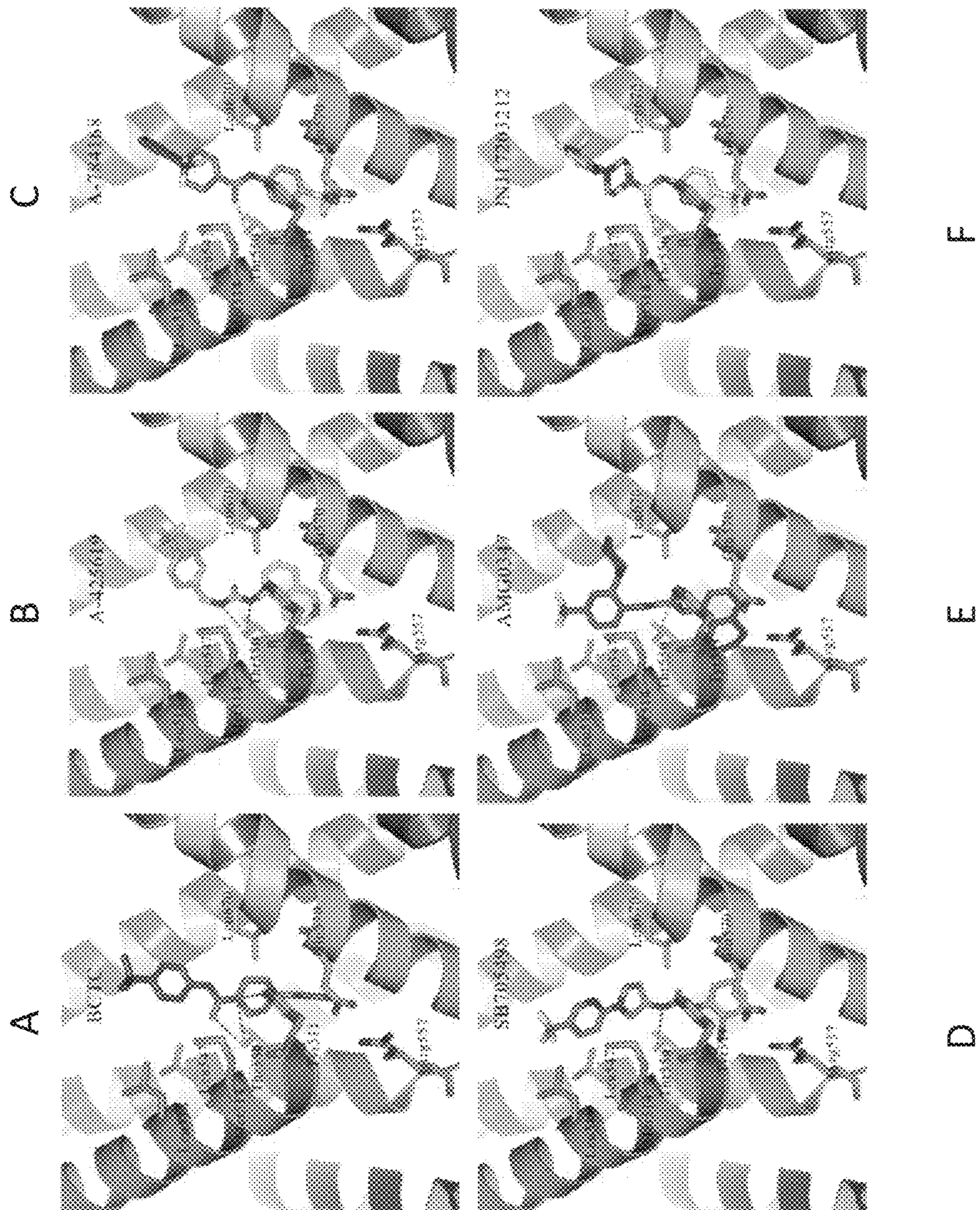
19 Claims, 20 Drawing Sheets

Specification includes a Sequence Listing.

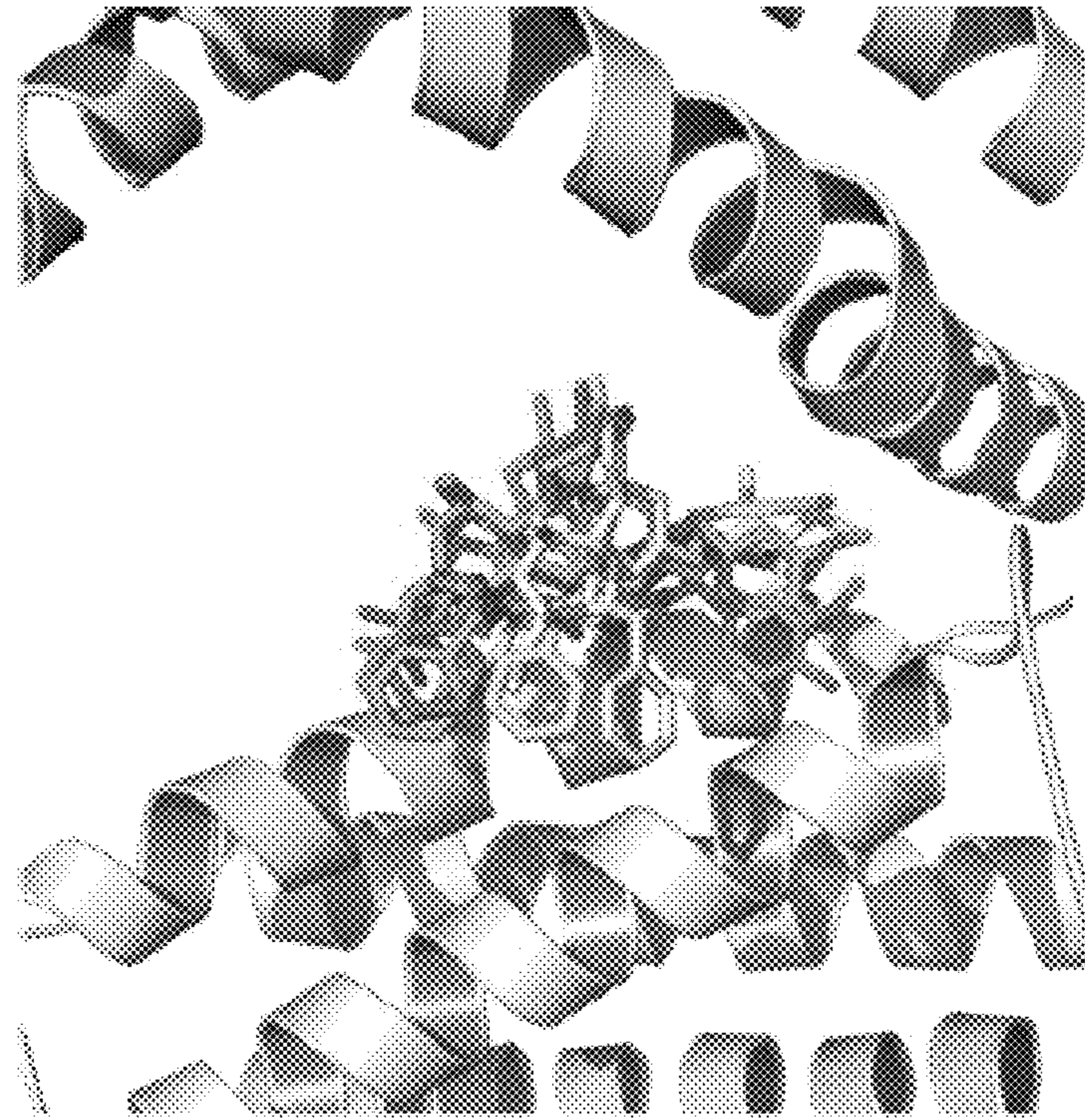
Figures 2A-2F



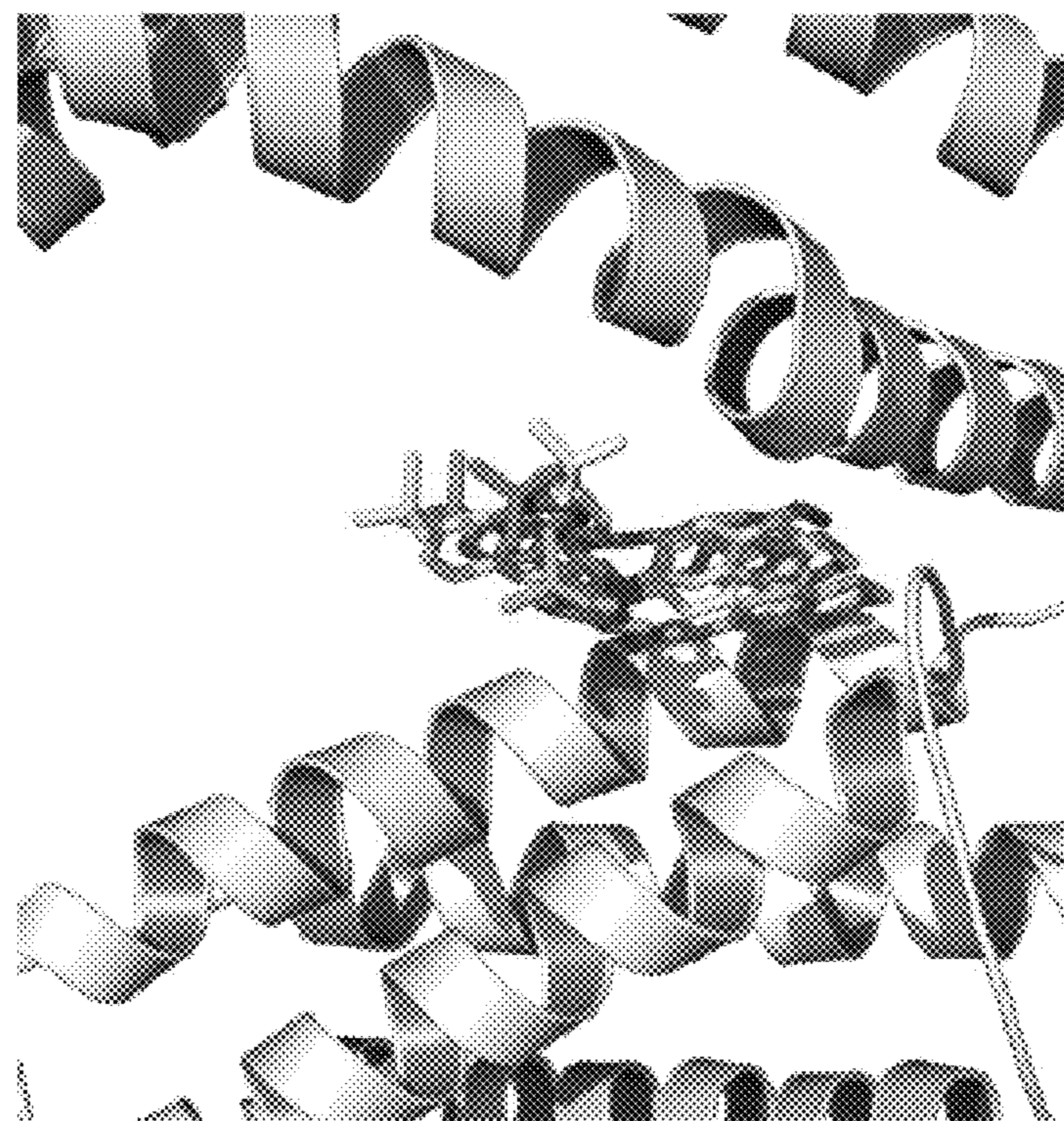
Figures 3A-3F



Figures 4A-4B



(B)



(A)

Figures 5A-5B

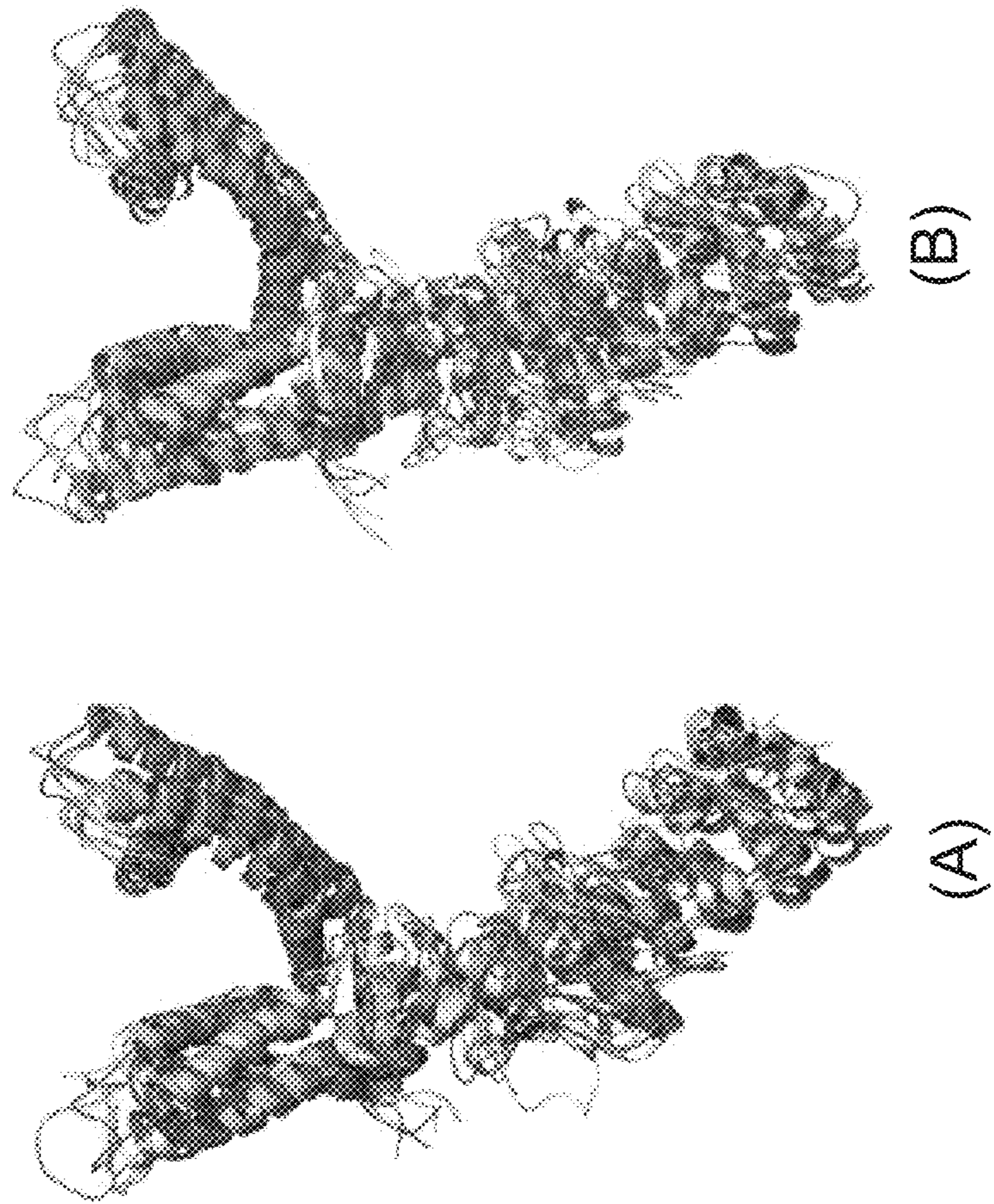


Figure 6



Figure 7

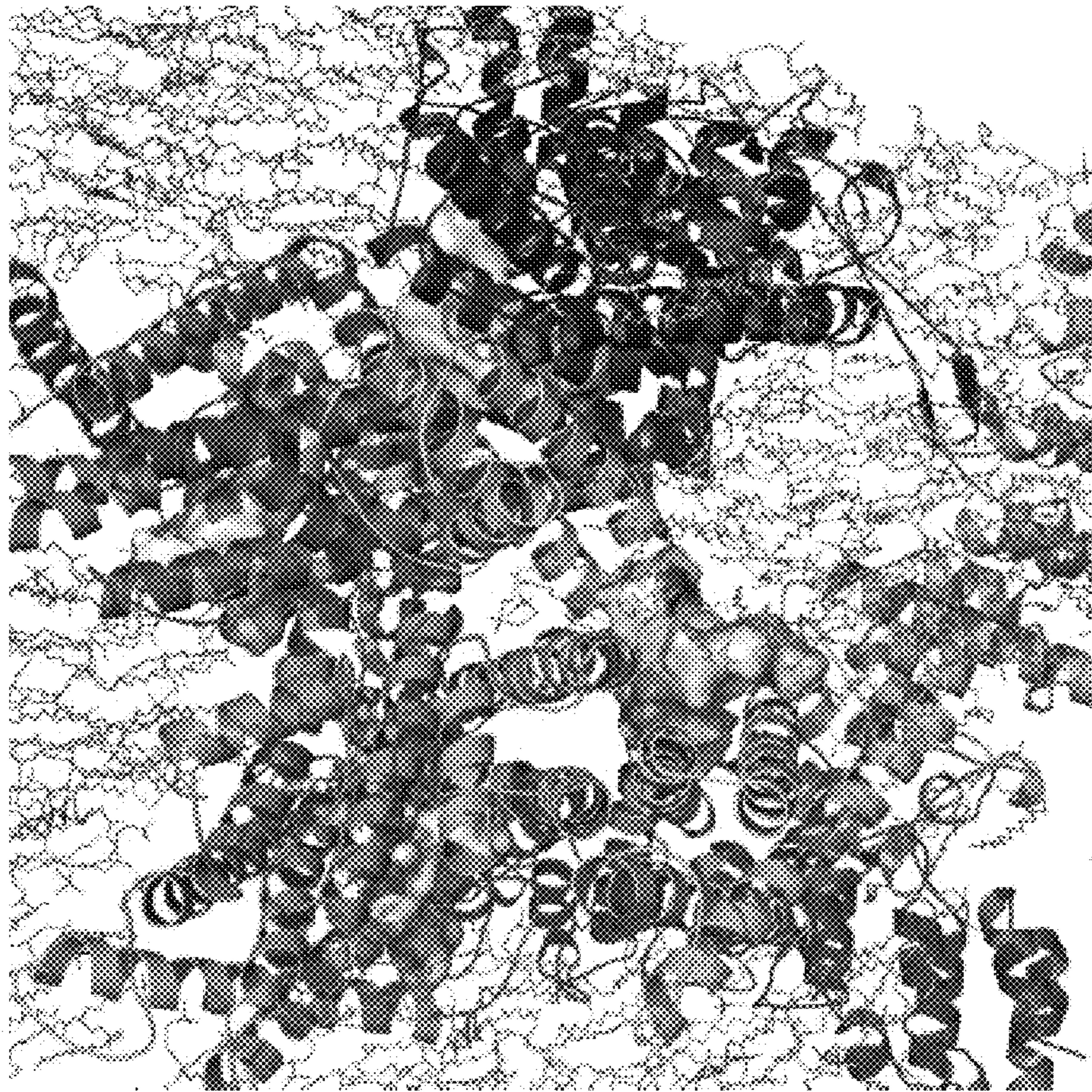


Figure 8

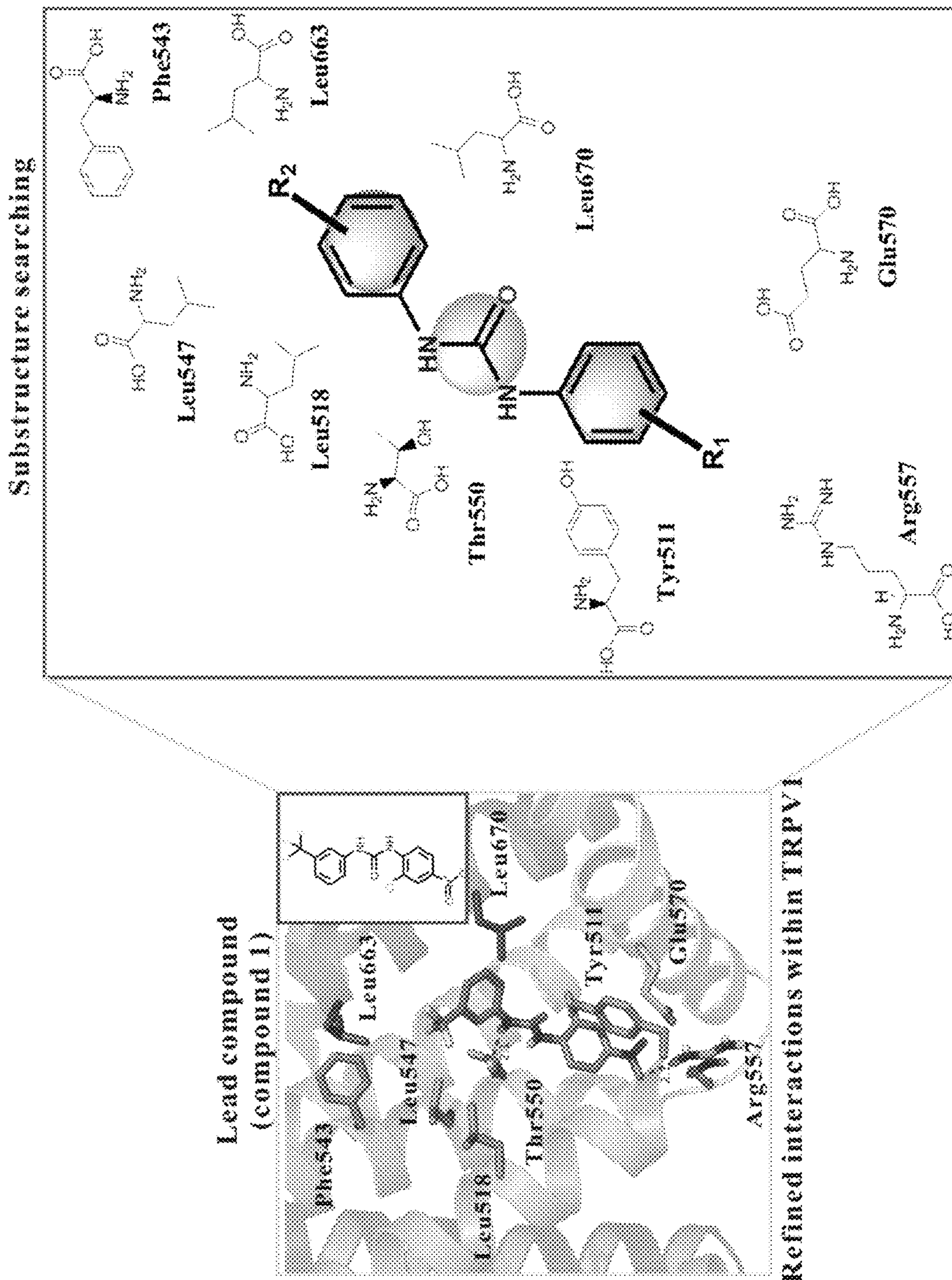
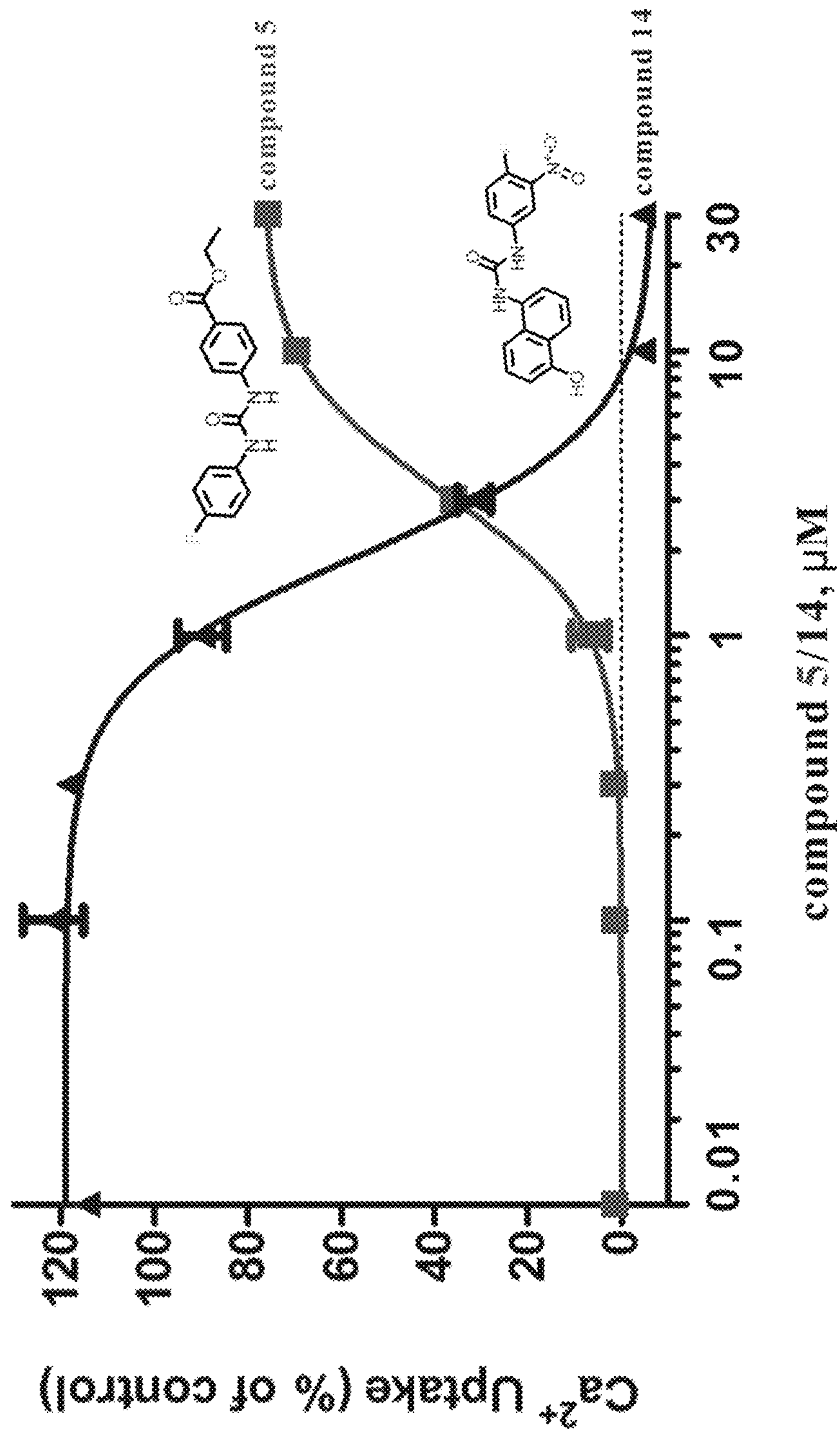
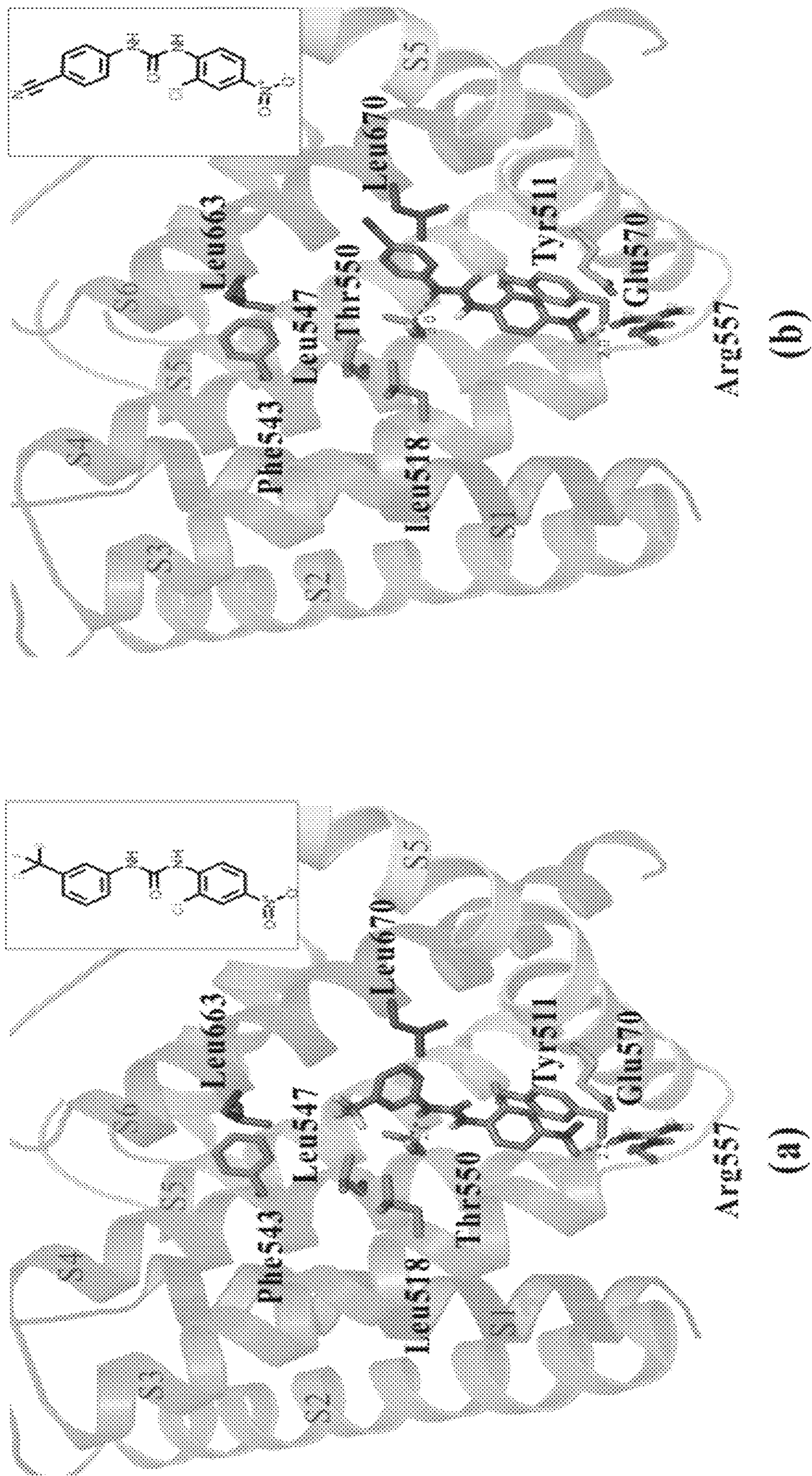


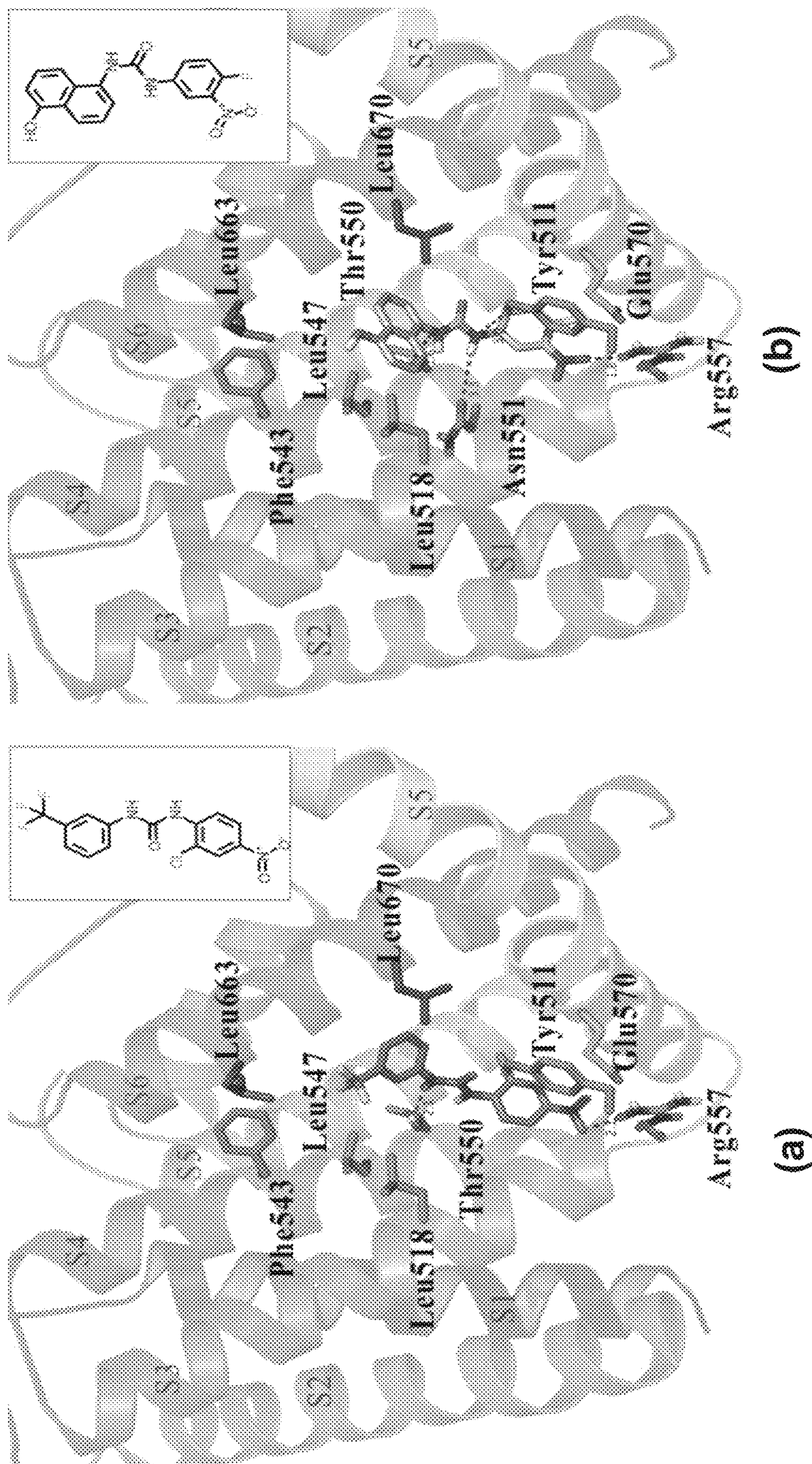
Figure 9



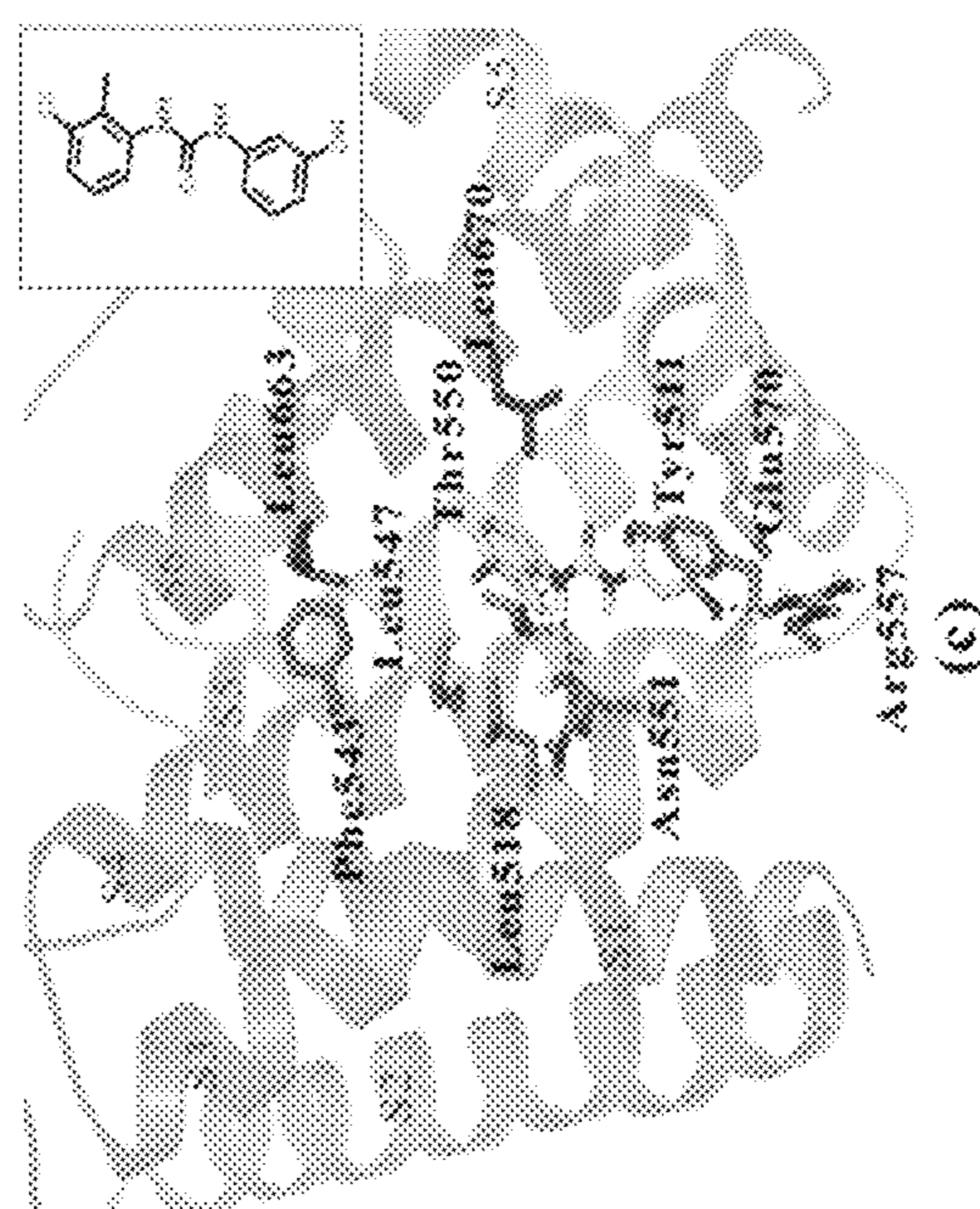
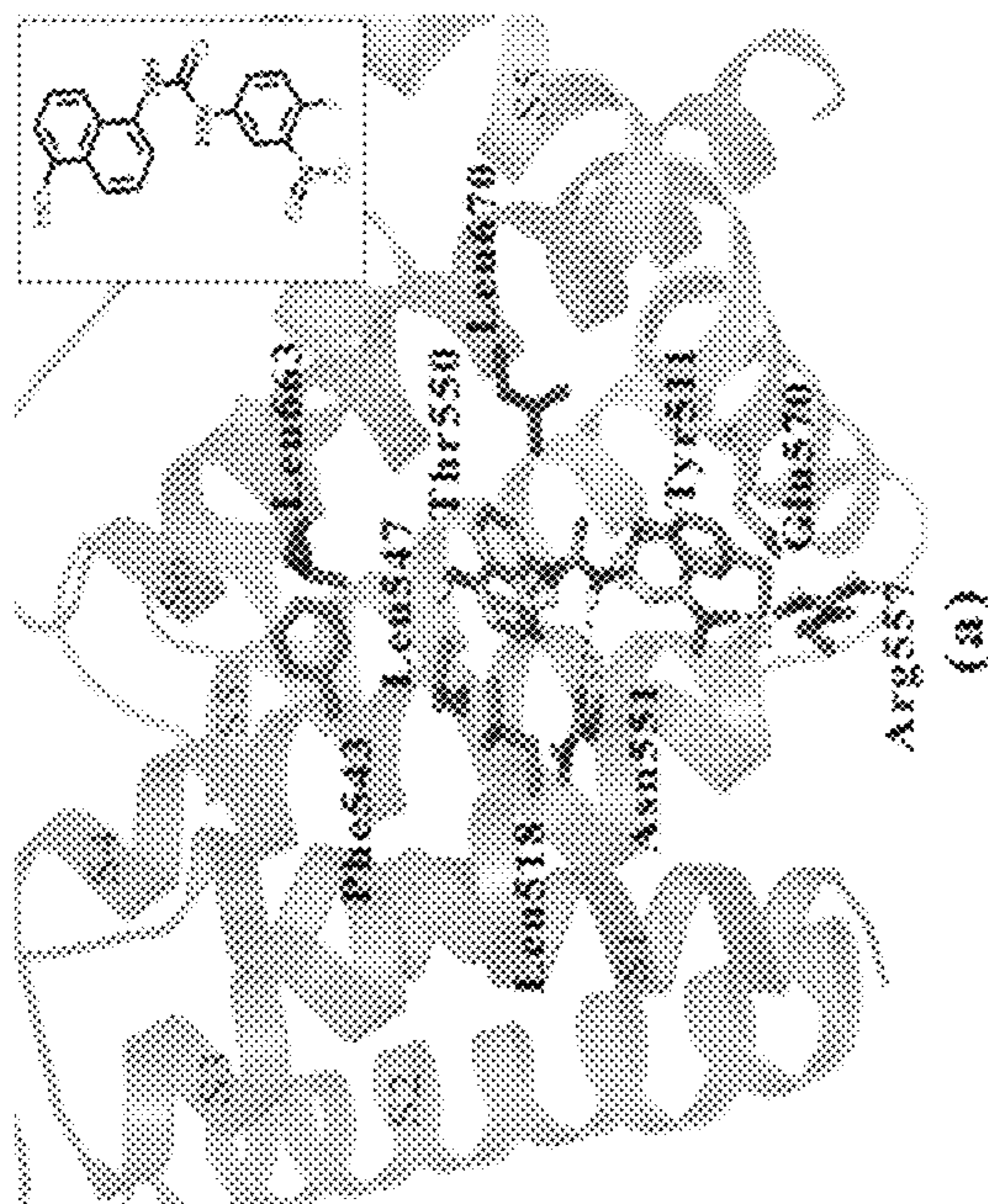
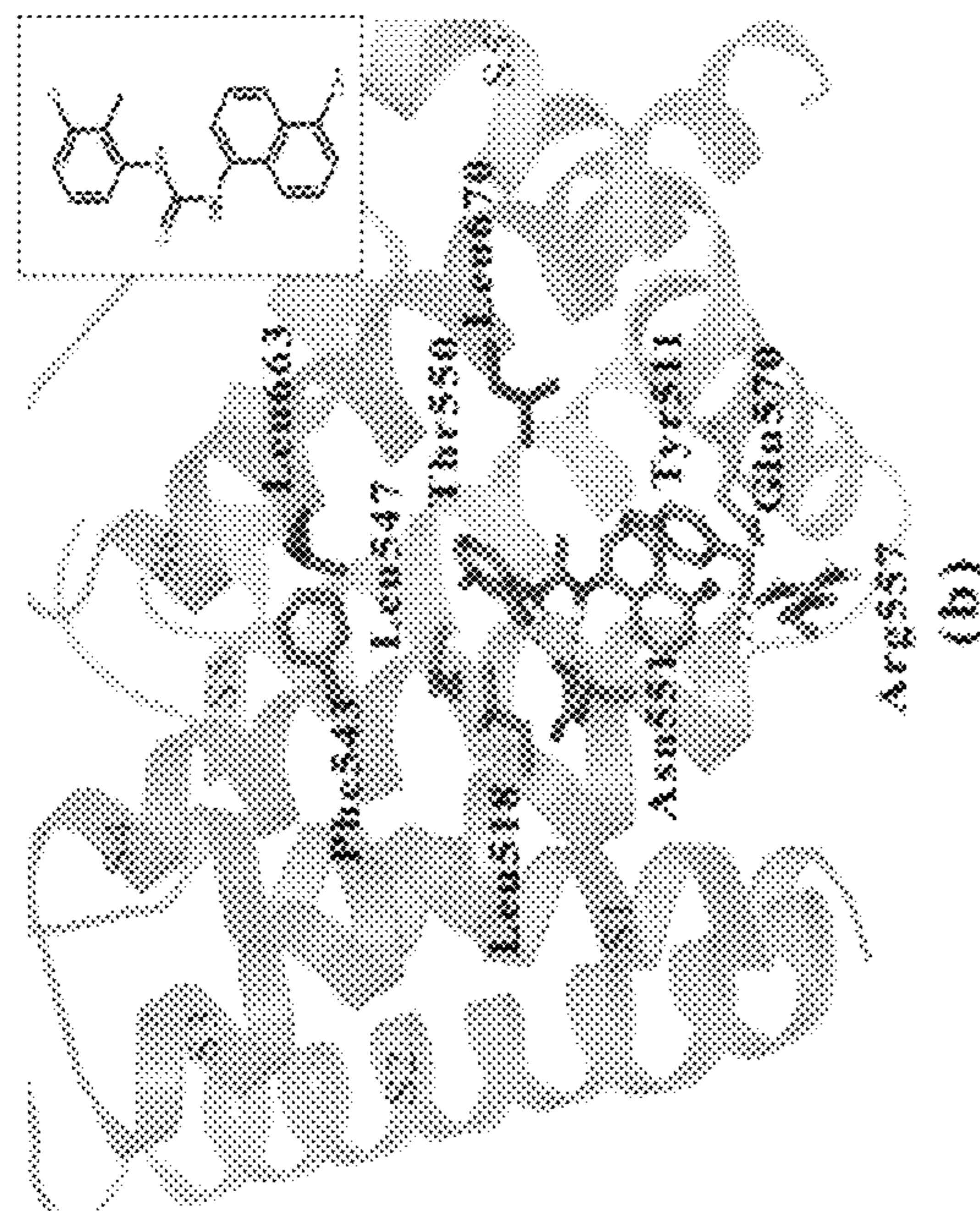
Figures 10A-10B



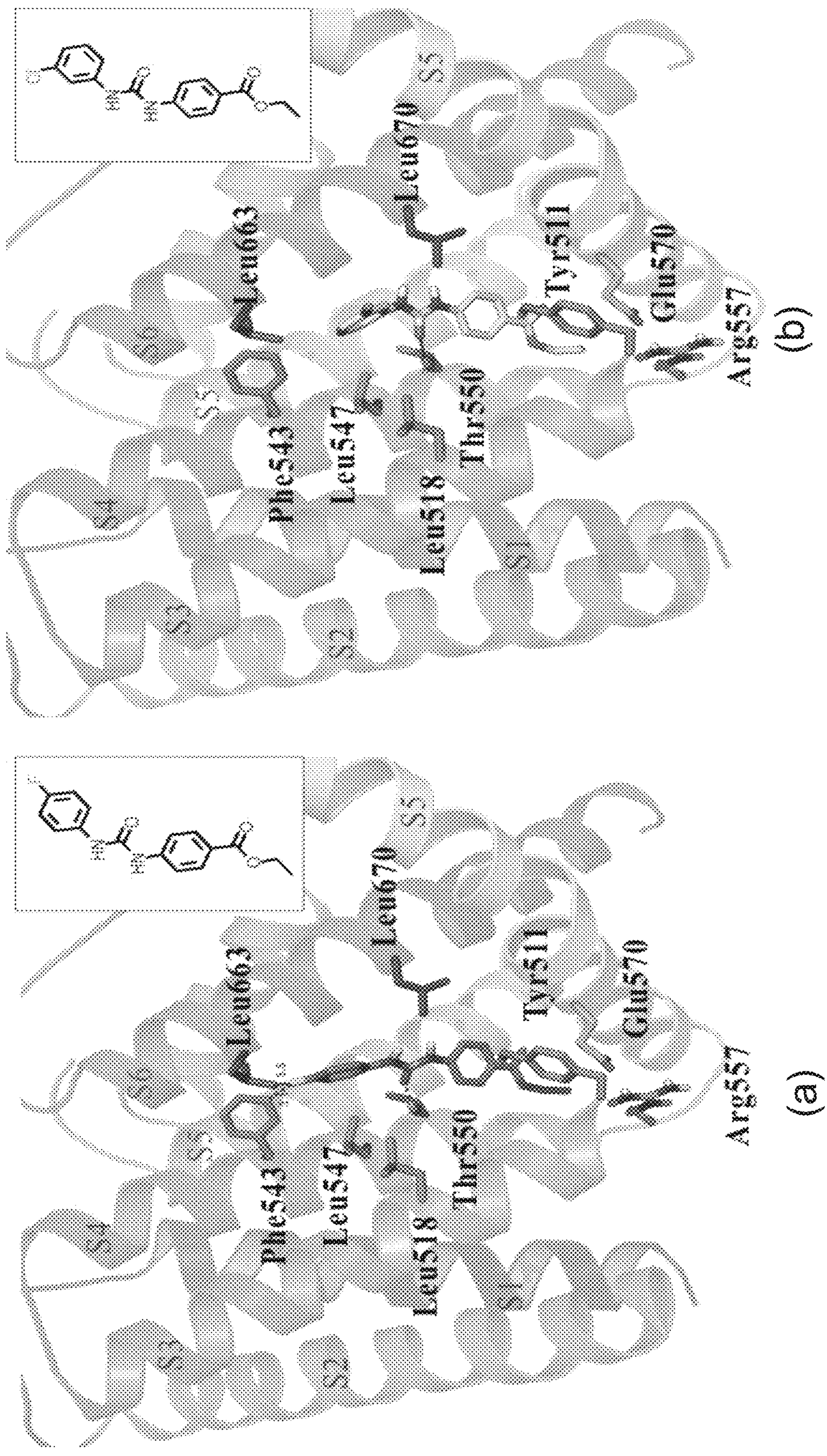
Figures 11A-11B



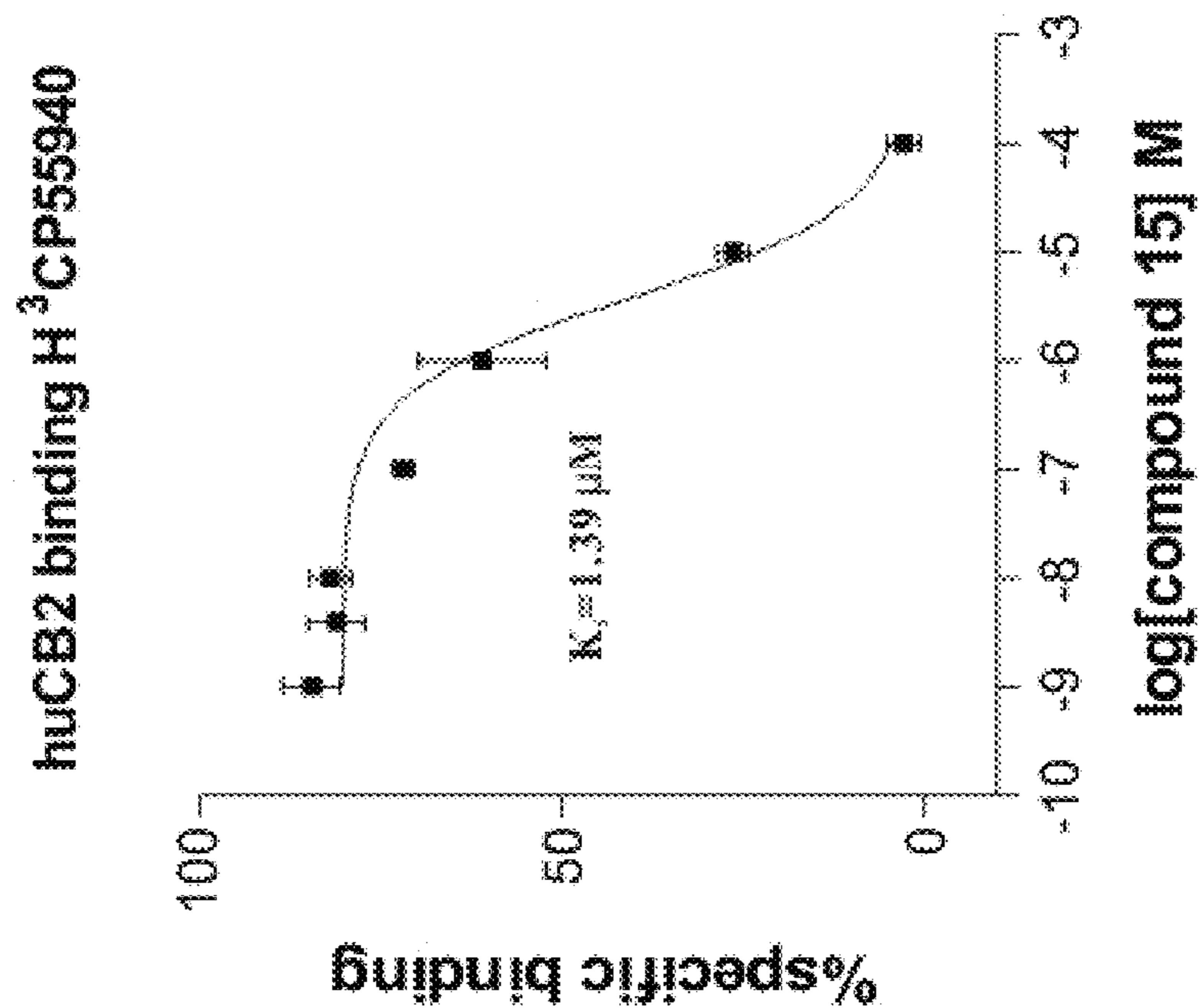
Figures 12A-12C



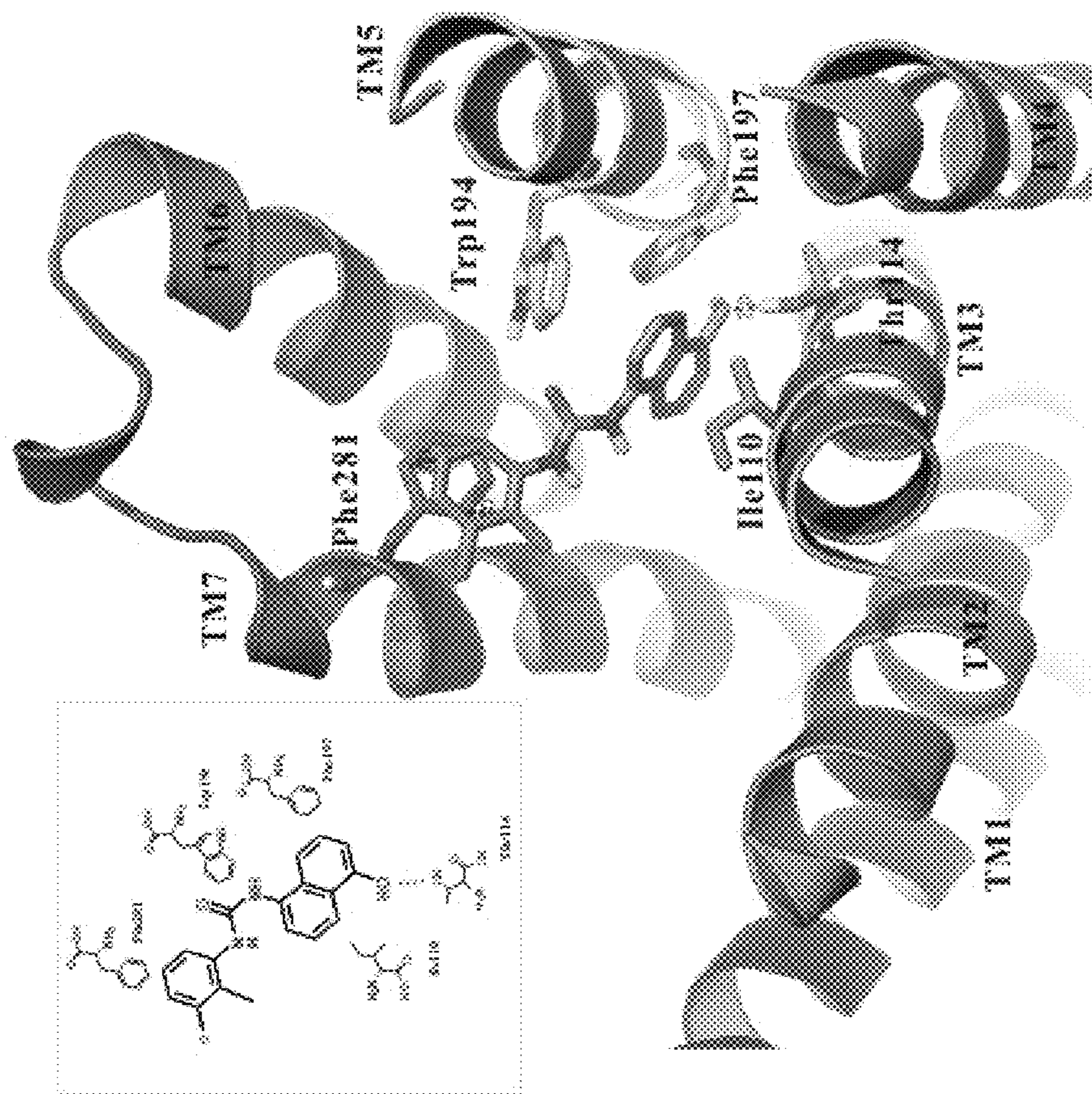
Figures 13A-13B



Figures 14A-14B

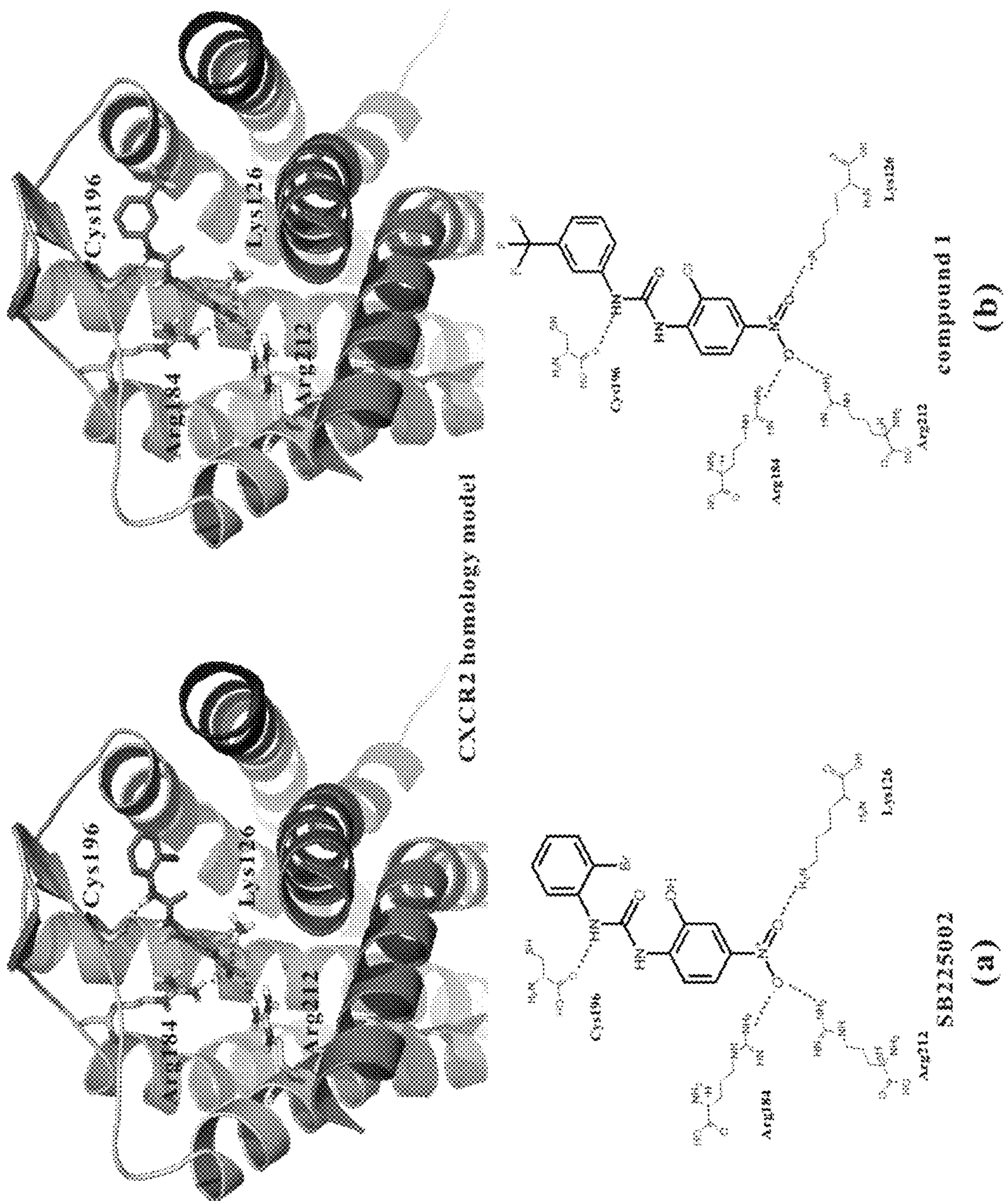


(a)

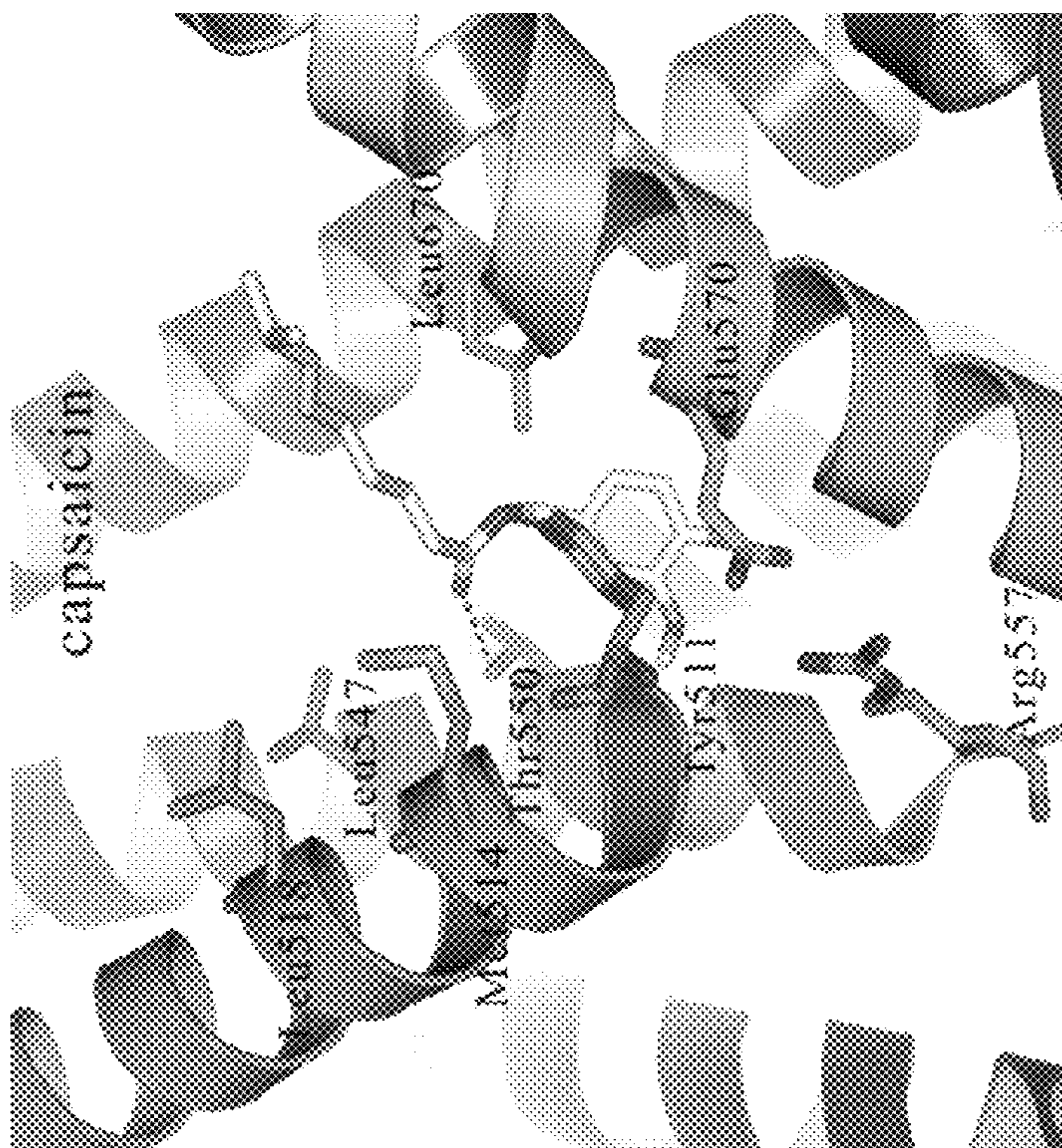


(b)

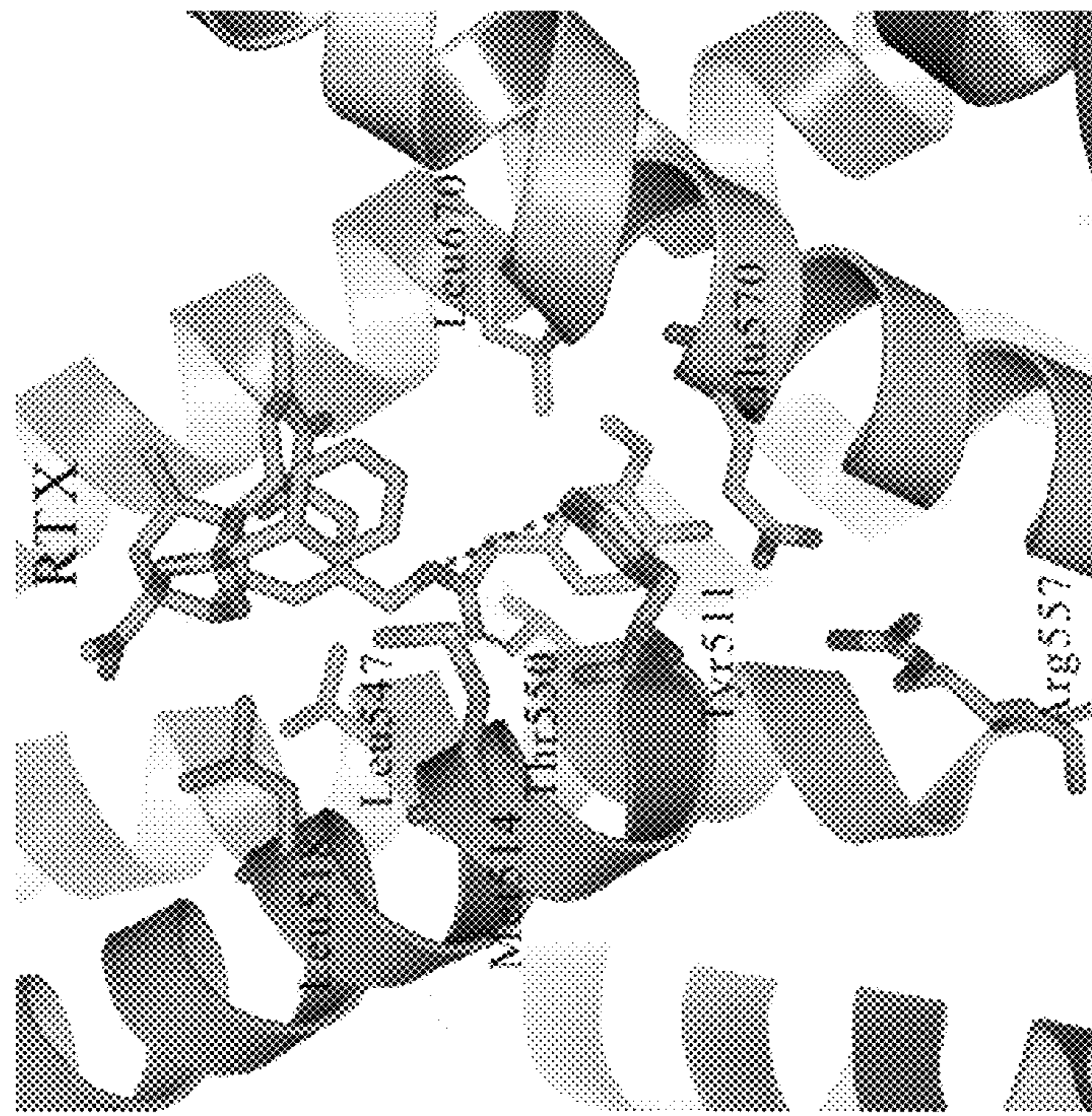
Figure 15



Figures 16A-16B



(a)



(b)

Figure 17

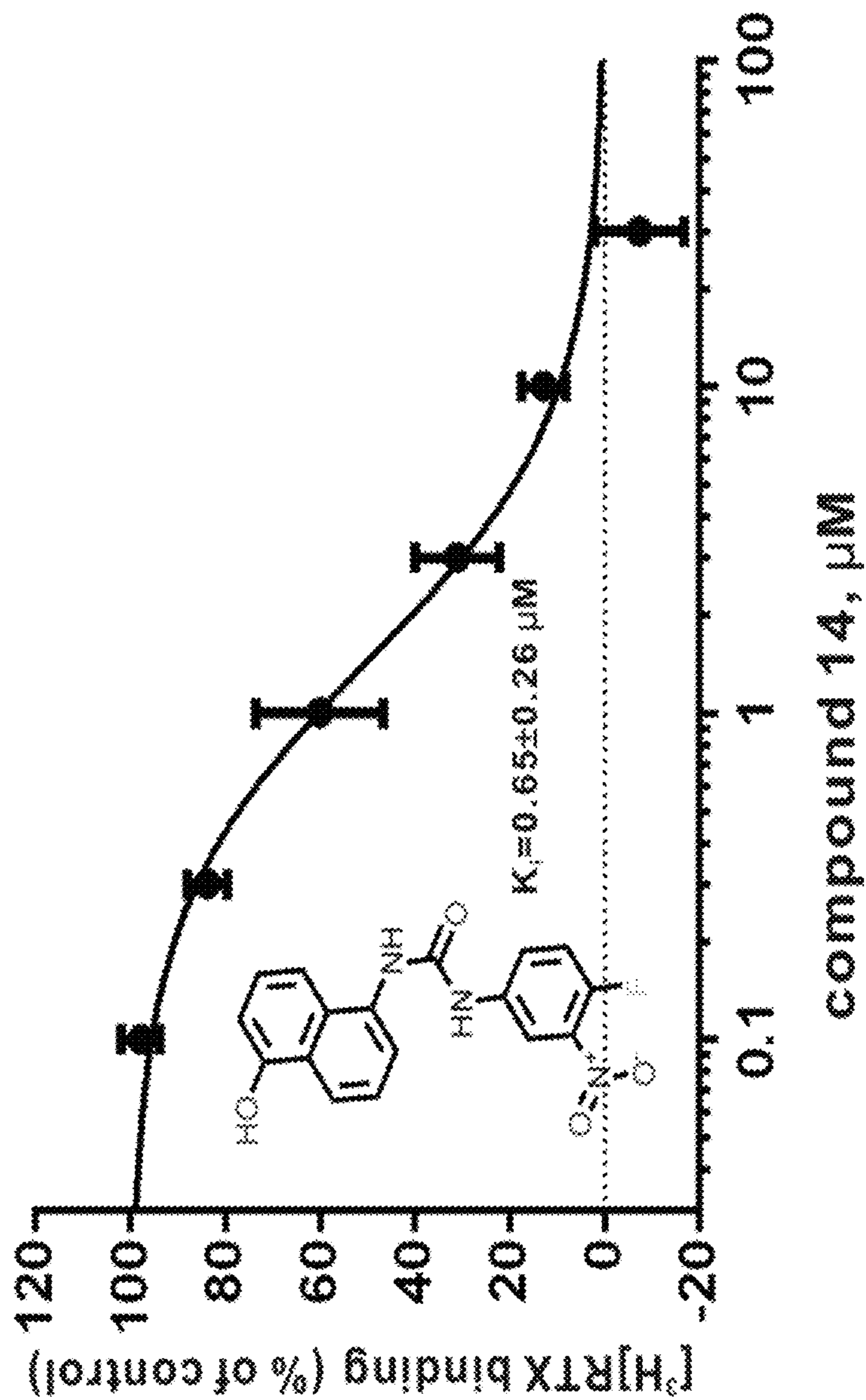


Figure 18

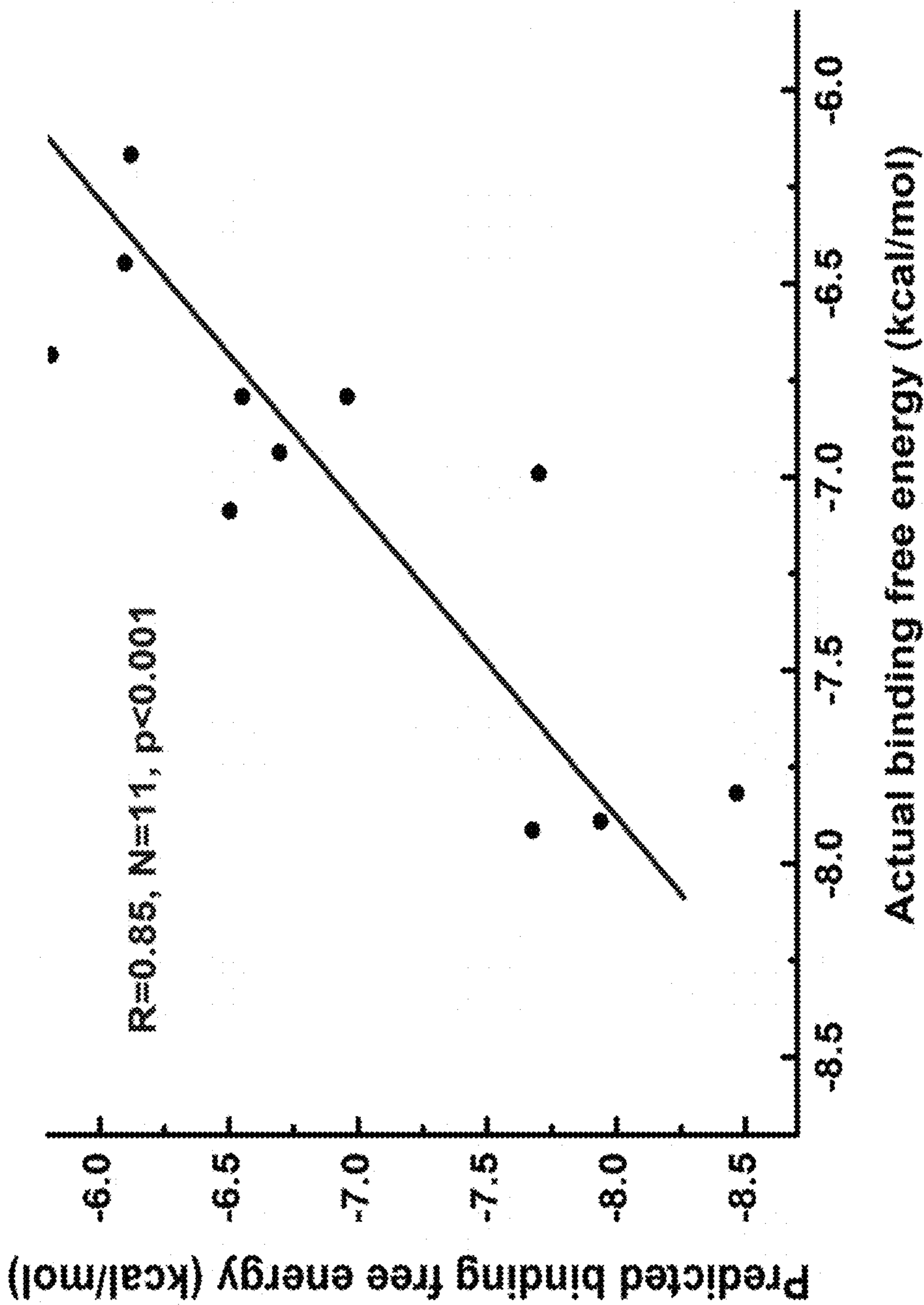
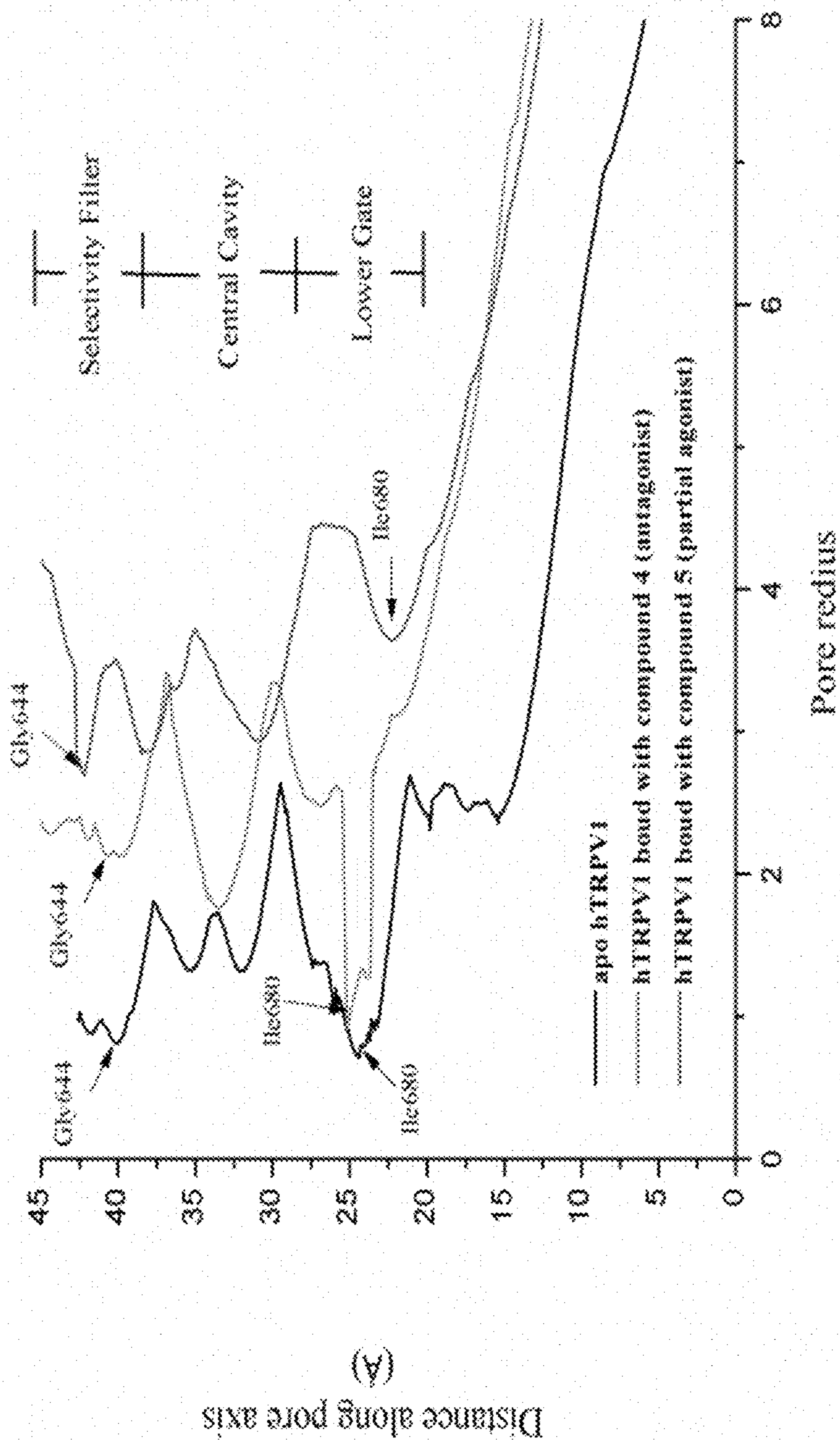
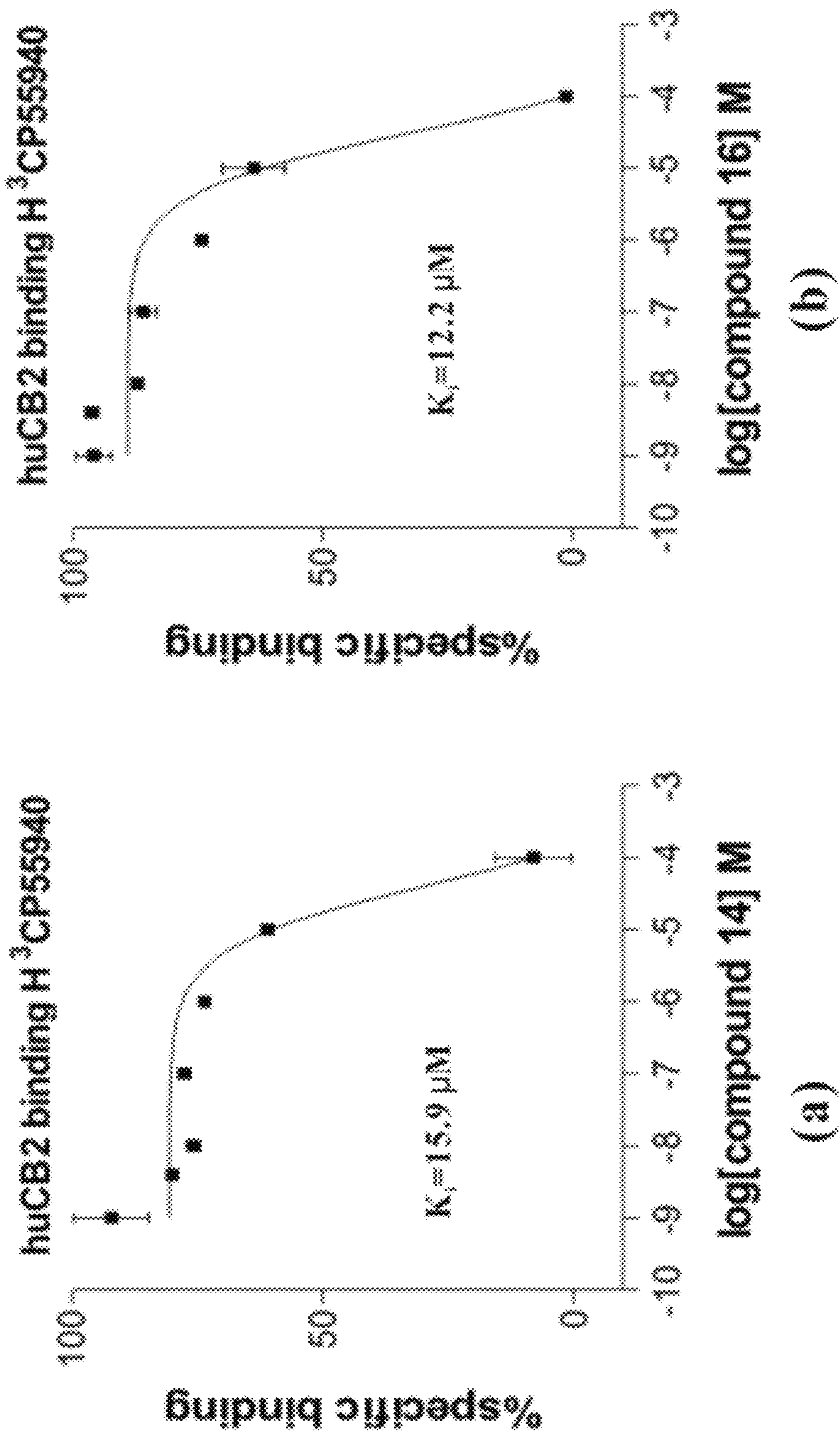


Figure 19



Figures 20A-20B



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HTRPV1 CHEMICAL AGENTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 15/546,833, filed Jul. 27, 2017, now U.S. Pat. No. 10,899,702, which is the U.S. National Stage of International Patent Application No. PCT/US2016/016826, filed Feb. 5, 2016, which claims priority from U.S. Provisional Patent Application No. 62/113,429, filed Feb. 7, 2015. The contents of these applications are incorporated herein by reference in their entirety.

STATEMENT OF GOVERNMENT SUPPORT

This invention was made with government support under NIH grant #DA025612 awarded by the NIH. The government has certain rights in the invention.

SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Dec. 4, 2017, is named 076333-0897_SL.txt and is 14,752 bytes in size.

BACKGROUND

Transient receptor potential (TRP) channels are among the largest families of ion channels. There are 28 known TRP cation channels in the TRP superfamily, which can be further subdivided into six subfamilies: TRPA (“Ankyrin”: TRPA1), TRPML (“Mucolipin”: TRPML1-TRPML3), TRPP (“Polycystin”: TRPP1-TRPP3), TRPM (“Melastatin”: TRPM1-TRPM8), TRPC (“Canonical”: TRPC1-TRPC7), and TRPV (“Vanilloid”: TRPV1-TRPV6).

Transient receptor potential vanilloid type 1 (TRPV1) is a member of the TRPV subfamily. TRPV1 and has been reported to contribute to acute and chronic pain, such as osteoarthritis, neuropathic pain, migraine, inflammatory bowel disease, and bone cancer pain. Brain TRPV1 is also postulated to have a pathogenic role in various neurological and psychiatric disorders, ranging from Parkinson’s disease, schizophrenia, and Alzheimer disease to anxiety, depression and other mood disorders.

Recently, the structures of *Rattus norvegicus* apo-TRPV1 (rTRPV1), rTRPV1 bound with RTX/DkTx or with capsaicin has been reported by using single particle electron cryo-microscopy. Cao et al., “TRPV1 Structures in Distinct Conformations Reveal Activation Mechanisms,” *Nature*, 504:113-118 (2013); Liao et al., “Structure of the TRPV1 Ion Channel Determined by Electron Cryo-Microscopy,” *Nature*, 504:107-11 (2013). Unfortunately, the resolution was insufficient to reveal in detail the nature of the ligand binding interactions with TRPV1.

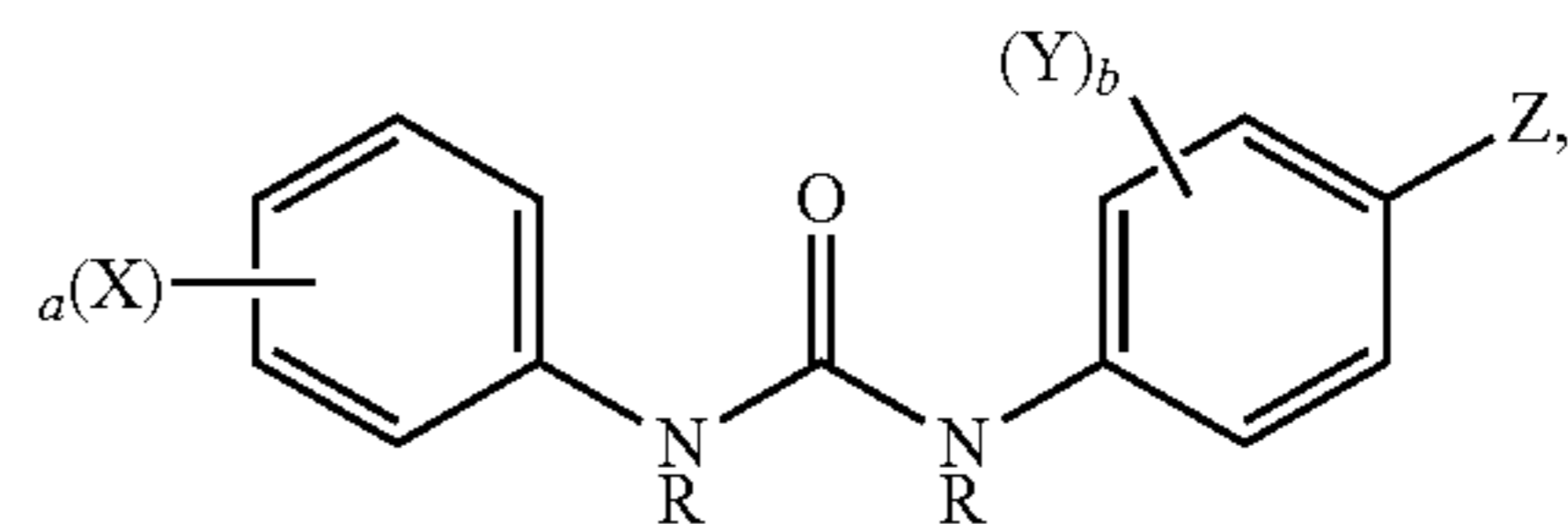
Human TRPV1 (hTRPV1) shares 85.7% sequence identity with rTRPV1. Most of the antagonists of hTRPV1, which represent the predominant therapeutic strategy for utilization of vanilloids in the treatment of pain, share a scaffold and R-groups. Developing antagonists of hTRPV1 has been hindered by the unavailability of the 3D structure of hTRPV1.

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Thus, there remains a need in the art to determine a pharmacophore model of hTRPV1. Furthermore, there remains a need in the art to develop new antagonists for hTRPV1.

SUMMARY OF THE INVENTION

One embodiment of the invention relates to a compound represented by Formula (I):



wherein:

X is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene; Y is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene; Z is halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene; R is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene; R' is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene.

alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene; a is an integer of 0 to 5; and b is an integer of 0 to 4, wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, Z is N(R')₂ or NO₂ and a is an integer of 1 to 5; and b is an integer of 0 to 4. In yet another embodiment, X is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl; Y is independently in each instance halogen, C₁-C₆ alkyl; Z is N(R')₂, NO₂; R is independently in each instance H, C₁-C₆ alkyl; R' is independently in each instance H, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl; a is an integer of 1 to 5; and b is an integer of 0 to 4, wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

In another embodiment, a and b are each independently an integer of 1 to 3, or a and b are one. In another embodiment, X is fluoro, C₁-C₆ alkyl or C₁-C₆ perfluoroalkyl and a is 1. In another embodiment, Y is a C₁-C₆ alkyl and b is 1. In another embodiment, R is H. In another embodiment, Z is NO₂.

Other aspects of the present invention include a pharmaceutical composition comprising a compound of any of the prior embodiments and at least one pharmaceutically acceptable carrier.

Another aspect of the present invention includes a method of treating pain associated with transient receptor potential vanilloid type 1 (TRPV1) in a subject in need thereof, comprising administering to the subject an effective amount of a compound or composition of any of the prior embodiments. In some embodiments, the pain associated with TRPV1 is selected from the group consisting of osteoarthritis, neuropathic pain, migraine, inflammatory bowel disease, and bone cancer pain.

Yet another aspect of the present invention includes a method of inhibiting the activity of TRPV1 comprising contacting TRPV1 with a compound or composition of any prior embodiments.

The foregoing general description and following description of the drawings and detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following brief description of the drawings and detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a sequence alignment between hTRPV1 (SEQ ID NO: 1) and rTRPV1 (SEQ ID NO: 2) in the present work.

FIGS. 2A-2F are Ramachandran plots of hTRPV1 model constructed by rTRPV1.

FIG. 2A=General case; FIG. 2B=isoleucine and valine; FIG. 2C=pre-proline; FIG. 2D=glycine; FIG. 2E=trans proline; and FIG. 2F=cis proline. 95.5% (554/580) of all residues were in favored regions. 99.1% (575/580) of all residues were in allowed regions. There were 5 outliers (phi, psi): Glu250 (56.0, -24.3), Leu385 (88.0, 72.8), Thr407 (88.0, -19.7), Asp459 (22.4, -126.2), Pro462 (-28.9, -68.7).

FIGS. 3A-3F show detailed binding modes of six other antagonists with hTRPV1, including BCTC (FIG. 3A), A-425619 (FIG. 3B), A-784168 (FIG. 3C), SB705498 (FIG. 3D), AMG0347 (FIG. 3E), and JNJ17203212 (FIG. 3F). Two residues, Tyr511 and Thr550, formed strong hydrogen bonds with the antagonists.

FIGS. 4A and 4B show alignments of (a) four AMG9810 and (b) of four RTX after MD simulation. The hTRPV1 and its compounds before MD simulation were highlighted in gray, while the four AMG9810 and four RTX in different monomers were highlighted in colors.

FIGS. 5A and 5B show alignments of four monomers (or units) (a) of hTRPV1 bound with AMG9810 and (b) of hTRPV1 bound with RTX.

FIG. 6 is alignments of hTRPV1 bound with AMG9810 and bound with RTX. hTRPV1 highlighted in green color was the structure of hTRPV1 bound with antagonist, while hTRPV1 highlighted in red color was the structure of hTRPV1 bound with agonist. Residues from 112 to 364 were hindered for clarity.

FIG. 7 shows four allosteric binding pockets in tetramer hTRPV1 model.

FIG. 8 shows a substructure search of diarylurea small molecules (derived from compound 1) against a refined compound library of 15,672 compounds for TRPV1.

FIG. 9 shows chemical structures and activity values of compounds 5 and 14. Compound 5 (partial agonist) yielded an EC₅₀ value for capsaicin agonism of 2.84±0.21 μM and maximal stimulation 55.7±7.8% of that by 3000 nM capsaicin (FIG. 9, red line). Compound 14 (antagonist) yielded a K_i value for capsaicin antagonism of 0.47±0.18 μM (FIG. 9, blue line) and inhibited [³H]RTX binding to hTRPV1 with a K_i value of 0.65±0.26 μM.

FIGS. 10a and 10b show a comparison of compound 1 with compound 10 indicating that the para-cyano replacement of a meta-trifluoromethyl R2 group affected the activity of the compounds at hTRPV1. (a) The detailed binding pose of compound 1 at TRPV1 (K_i: 2.57±0.62 μM). (b) The detailed binding pose of compound 10 at hTRPV1 (35±5% inhibition at 30 μM).

FIGS. 11a and 11b show a comparison of compound 1 with compound 14 indicating that the bulky R2 group replacement enhanced the activity of the ligand at hTRPV1. (a) The detailed binding pose of compound 1 at hTRPV1 (K_i: 2.57±0.62 μM). (b) The detailed binding pose of compound 14 at TRPV1 (K_i: 0.47±0.18 μM).

FIGS. 12a-12c show a comparison of compounds 14-16 indicating that the nitro/hydroxyl group in R1 was important for the activity of inhibitors at hTRPV1. (a) The detailed binding pose of compound 14 at TRPV1 (K_i: 0.47±0.18 μM). (b) The detailed binding pose of compound 15 at TRPV1 (K_i: 0.49±0.14 μM). (c) The detailed binding pose of compound 16 at TRPV1 (K_i: 0.56±0.16 μM).

FIGS. 13a and 13b show a comparison of the slight different binding modes of compound 5 (partial agonist) and compound 4 (antagonist) at hTRPV1. (a) The detailed binding pose of compound 5 at hTRPV1 (EC₅₀: 2.84±0.21 μM). (b) The detailed binding pose of compound 4 at hTRPV1 (K_i: 11.7±1.3 μM).

FIGS. 14a and 14b show that compound 15 of TRPV1 had potential binding at CB2. (a) The binding curve (K_i: 1.39 μM) of compound 15 at CB2. (b) The detailed binding pose of compound 15 at CB2.

FIG. 15 shows that compound 1 of TRPV1 is predicted to target CXCR2. The potential binding pose of the CXCR2 selective compound SB225002. (b) The potential binding pose of compound 1 at CXCR2. In vitro binding assays are still needed to experimentally validate the predicted binding activity of our compounds with CXCR2.

FIGS. 16a and 16b show detailed binding modes of (a) capsaicin and (b) RTX with hTRPV1. Two residues, Tyr511 and Thr550, formed hydrogen bonds with the agonists.

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FIG. 17 shows compound 14 inhibited [³H]RTX binding to hTRPV1 with a K_i value of $0.65 \pm 0.26 \mu\text{M}$.

FIG. 18 shows a correlation between the values for the predicted ΔG of the binding based on the modeling and the AG derived from the experimental activities (K_i) of the 11 compounds in the present work. We converted the experimental activities (K_i) to ΔG_{actual} (x-axis) using the equation $\Delta G_{actual} = RT \ln K_i$ (R: gas constant R, 8.314 J/mol*K; T: absolute temperature, $273.15 + 37 = 310.15\text{K}$, since the T for the binding was measured at 37°C .), comparing with the predicted $\Delta G_{predicted}$ (y-axis).

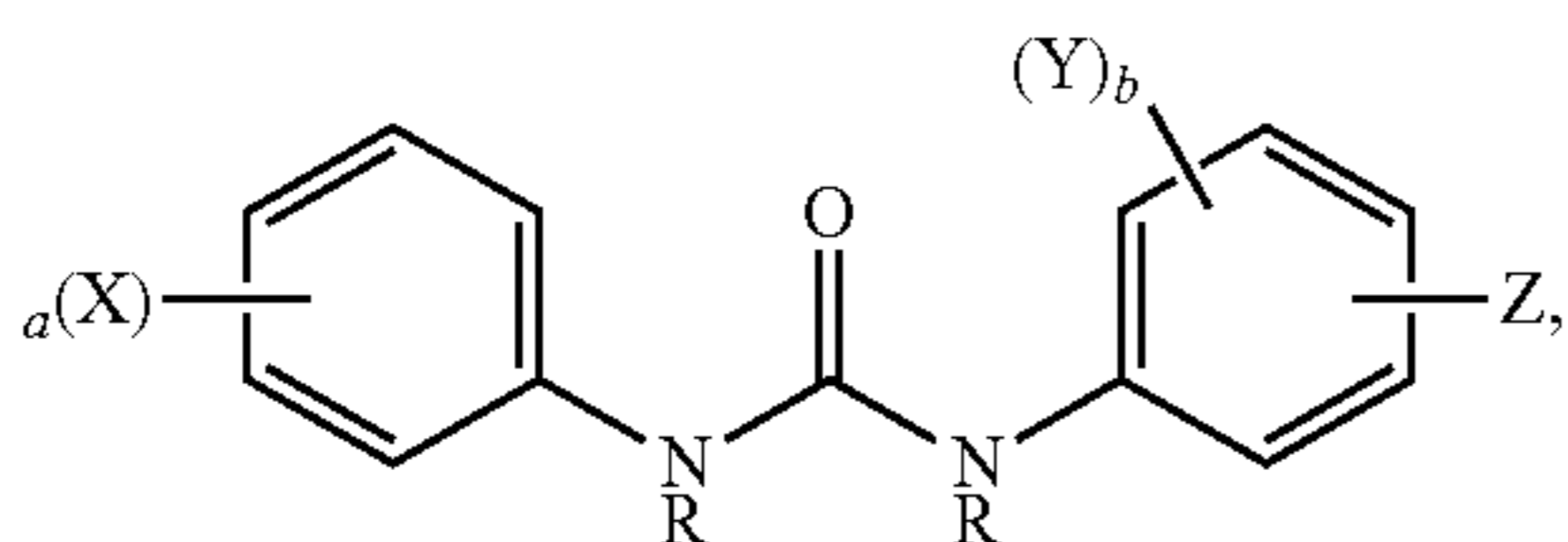
FIG. 19 shows the comparisons of pore radius and conformational changes of hTRPV1 bound with compound 4 and bound with compound 5. The pore radius along the channel for apo hTRPV1, hTRPV1-compound 4 (average conformation during the last 2 ns), and hTRPV1-compound 5 (average conformation during the last 2 ns).

FIGS. 20a and 20b show compounds (a) 14 and (b) 16 had weak binding activity with K_i values of 15.9 and 12.2 μM at CB2.

DETAILED DESCRIPTION

Compounds of the Invention

Compounds of the present disclosure include novel compounds represented by Formula (I):



wherein:

X is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₆)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Y is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₆)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Z is halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-

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C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R is independently in each instance H, -OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R' is independently in each instance H, -OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

a is an integer of 0 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen,

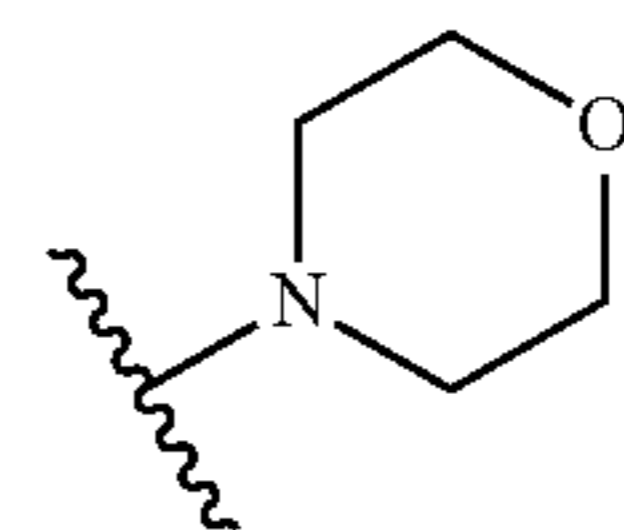
or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, in Formula (I),

X is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, N(R')₂, C₁-C₆ alkyloxy, pyrrolidine;

Y is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, N(R')₂, C₁-C₆ alkyloxy, pyrrolidine;

Z is N(R')₂, NO₂ or



R is independently in each instance H, C₁-C₆ alkyl;

R' is independently in each instance H, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl;

a is an integer of 1 to 5; and

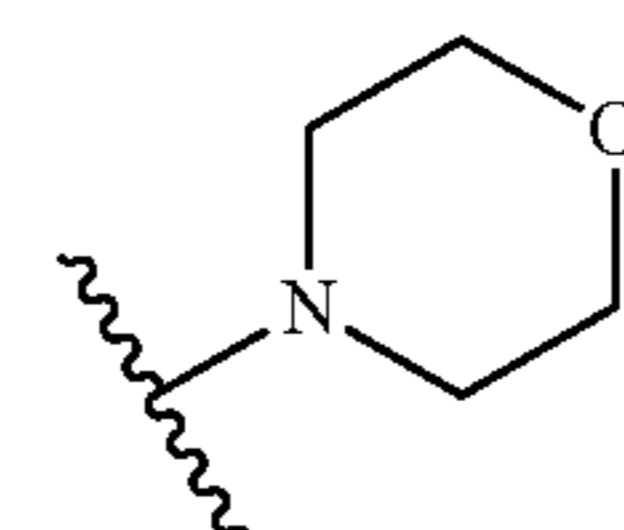
b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or

any pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the halogen is fluoro.

In some embodiments, Z is N(R')₂ or NO₂ or

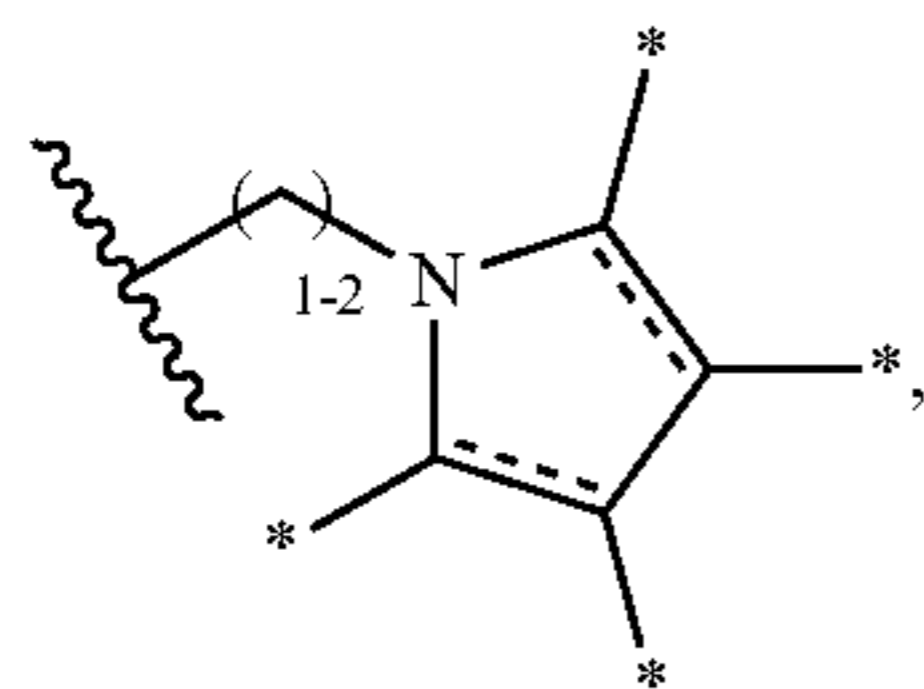


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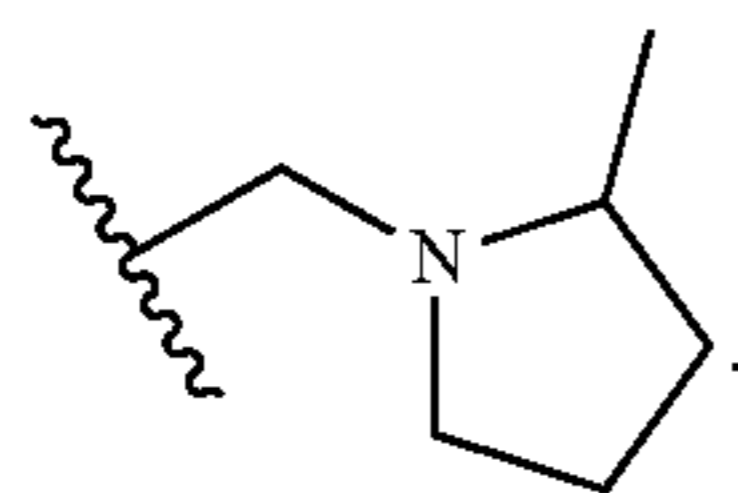
in the para or meta position. In some embodiments, Z is a para F or Cl moiety.

In some embodiments, a is an integer of 1 to 5; and b is an integer of 0 to 4.

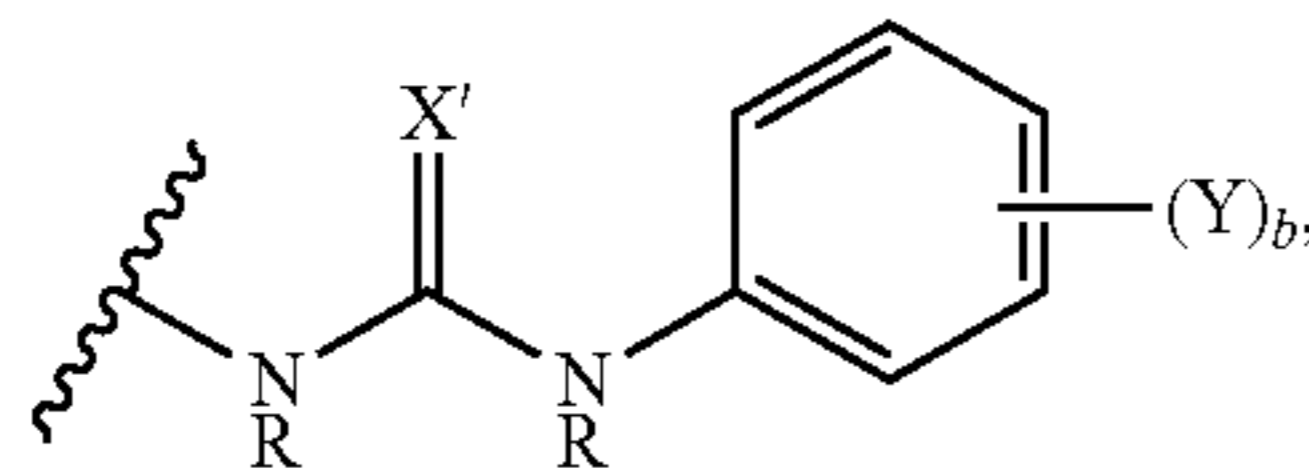
In some embodiments, X is



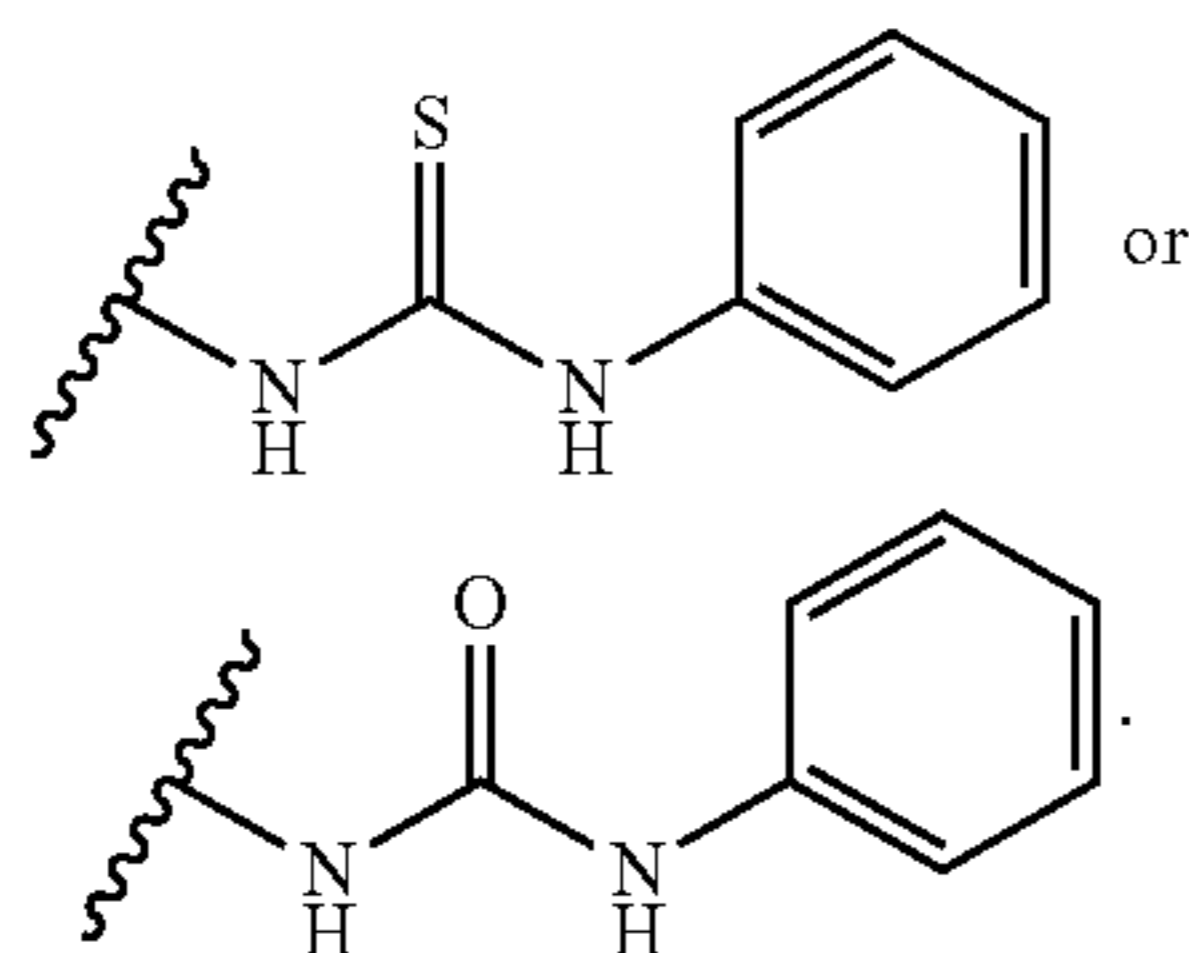
where --- represents an optional bond; * is independently H, D, Cl, F, Me, Et, OMe, or CF_3 , for example,



In some embodiments, X is

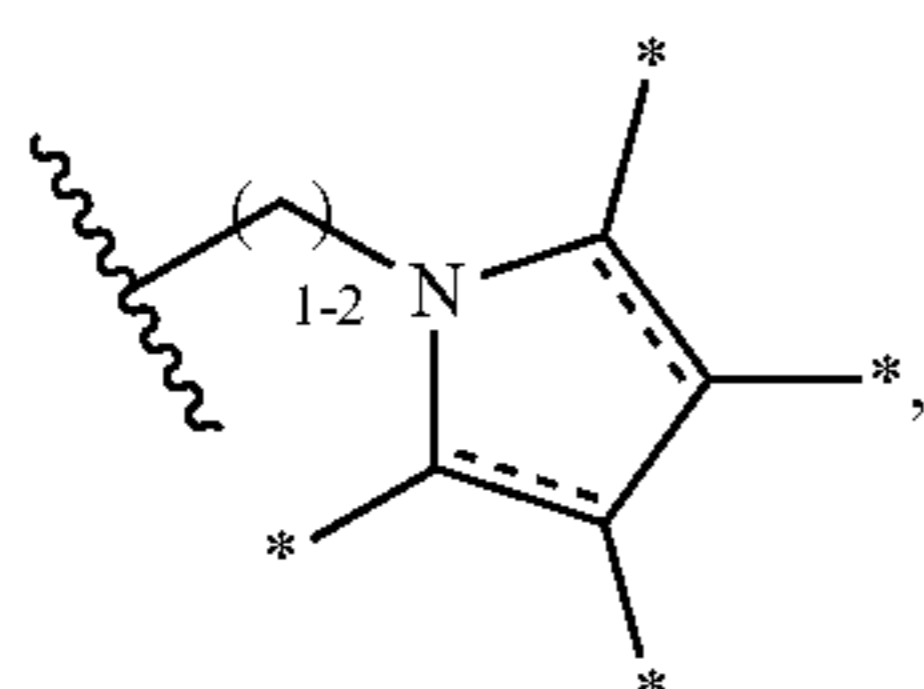


where X' is O or S, and R, Y and b are defined above, for example,



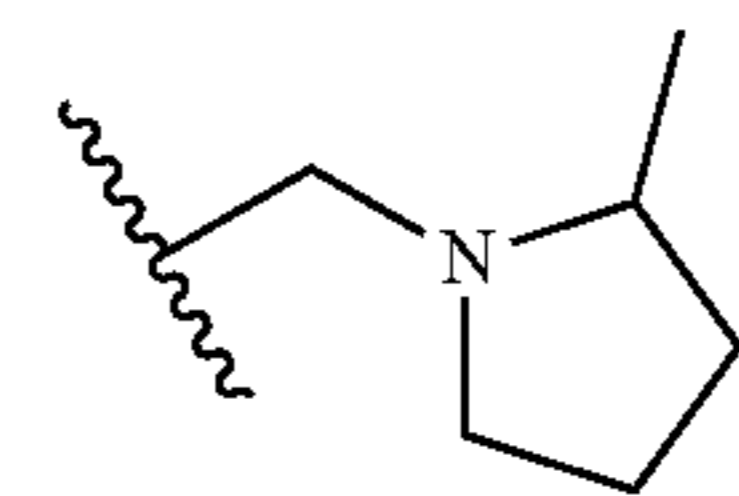
In some embodiments, X is selected from the group consisting of D, Cl, F, $(\text{CH}_2)_{0-5}\text{CH}_3$, (e.g., Me, Et), OMe, CF_3 , CN, $\text{C}(\text{O})\text{NR}_2$, $\text{COO}(\text{CH}_2)_{0-5}\text{CH}_3$, $\text{COO}(\text{CH}_2)_{0-5}\text{CF}_3$, $(\text{CH}_2)_{1-5}\text{OH}$, $(\text{CH}_2)_{0-5}\text{---O---}(\text{CH}_2)_{1-5}$, $(\text{CH}_2)_{0-5}\text{---S---}(\text{CH}_2)_{1-5}$, and $(\text{CH}_2)_{0-5}\text{---NR---}(\text{CH}_2)_{1-5}$.

In some embodiments, Y is



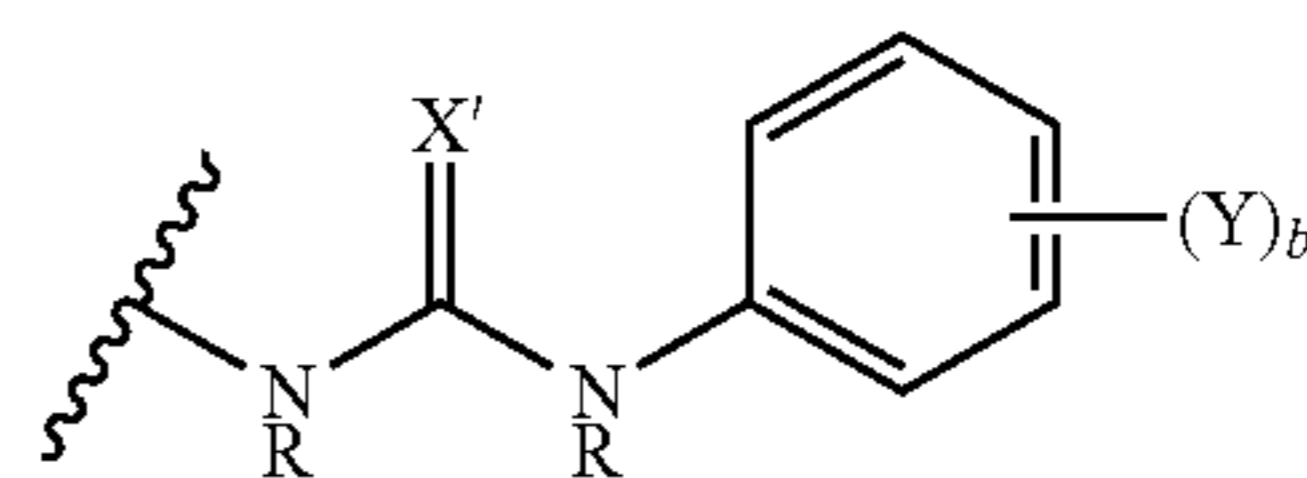
where --- represents an optional bond; * is independently H, D, Cl, F, Me, Et, OMe, or CF_3 , for example,

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In some embodiments, Y is

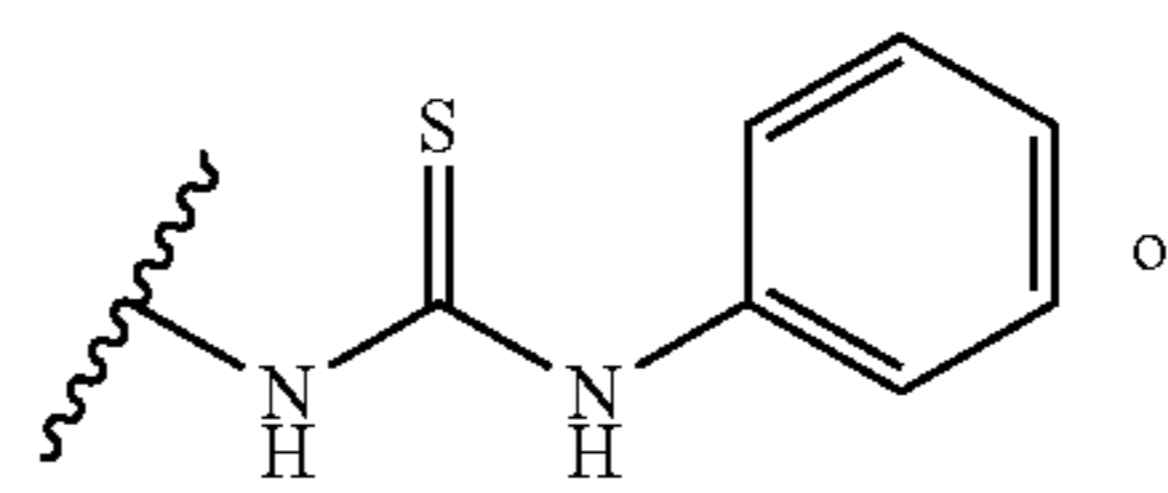


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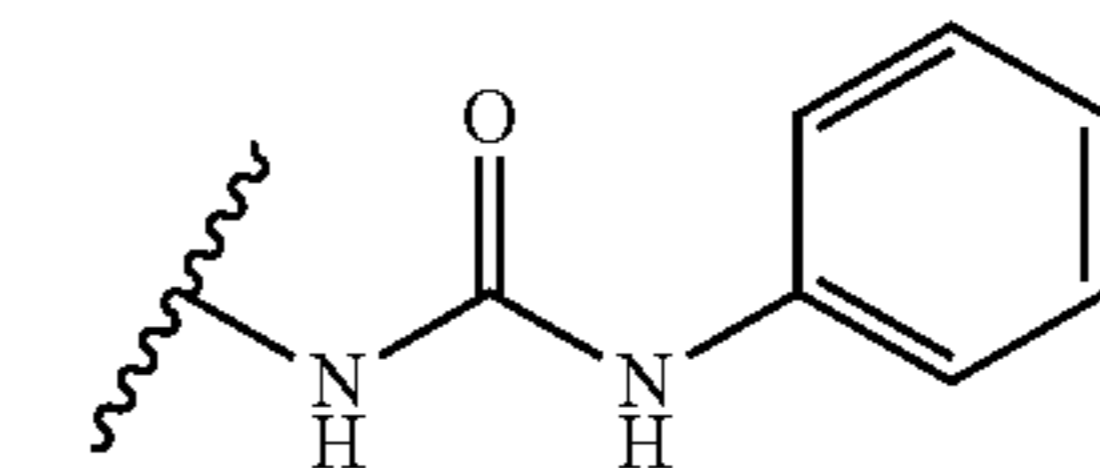
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where X' is O or S, and R, Y and b are defined above, for example,

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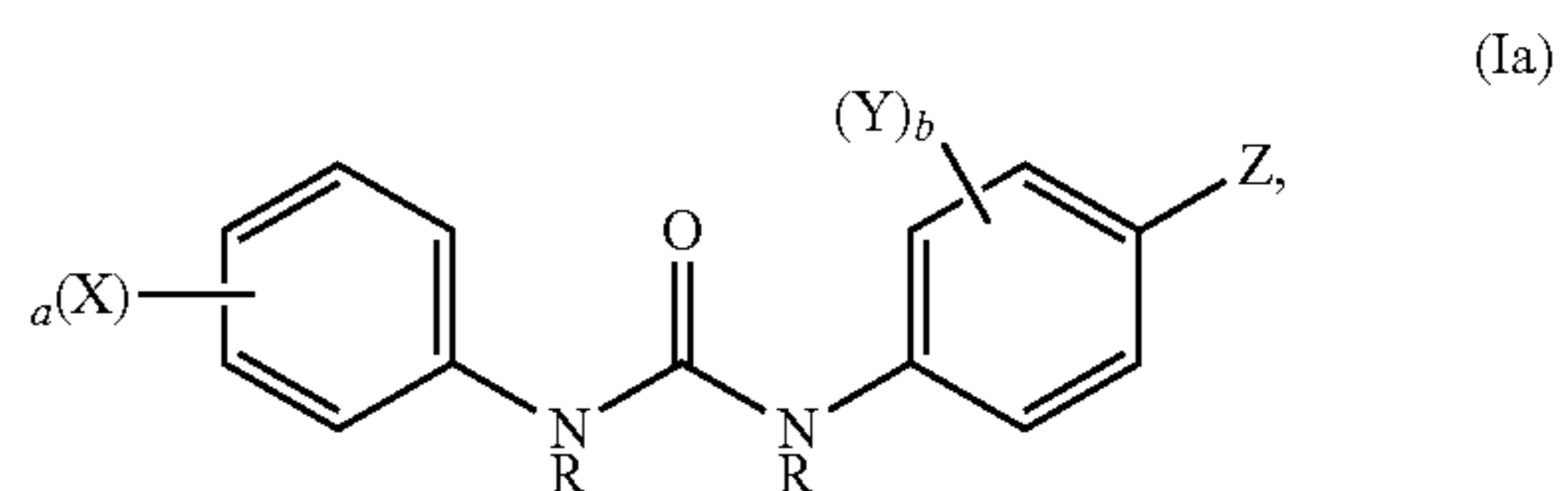
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In some embodiments, Y is selected from the group consisting of D, Cl, F, $(\text{CH}_2)_{0-5}\text{CH}_3$, (e.g., Me, Et), OMe, CF_3 , CN, $\text{C}(\text{O})\text{NR}_2$, $\text{COO}(\text{CH}_2)_{0-5}\text{CH}_3$, $\text{COO}(\text{CH}_2)_{0-5}\text{CF}_3$, $(\text{CH}_2)_{1-5}\text{OH}$, $(\text{CH}_2)_{0-5}\text{---O---}(\text{CH}_2)_{1-5}$, $(\text{CH}_2)_{0-5}\text{---S---}(\text{CH}_2)_{1-5}$, and $(\text{CH}_2)_{0-5}\text{---NR---}(\text{CH}_2)_{1-5}$.

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In some embodiments, the compounds of the present disclosure include novel compounds represented by Formula (Ia):

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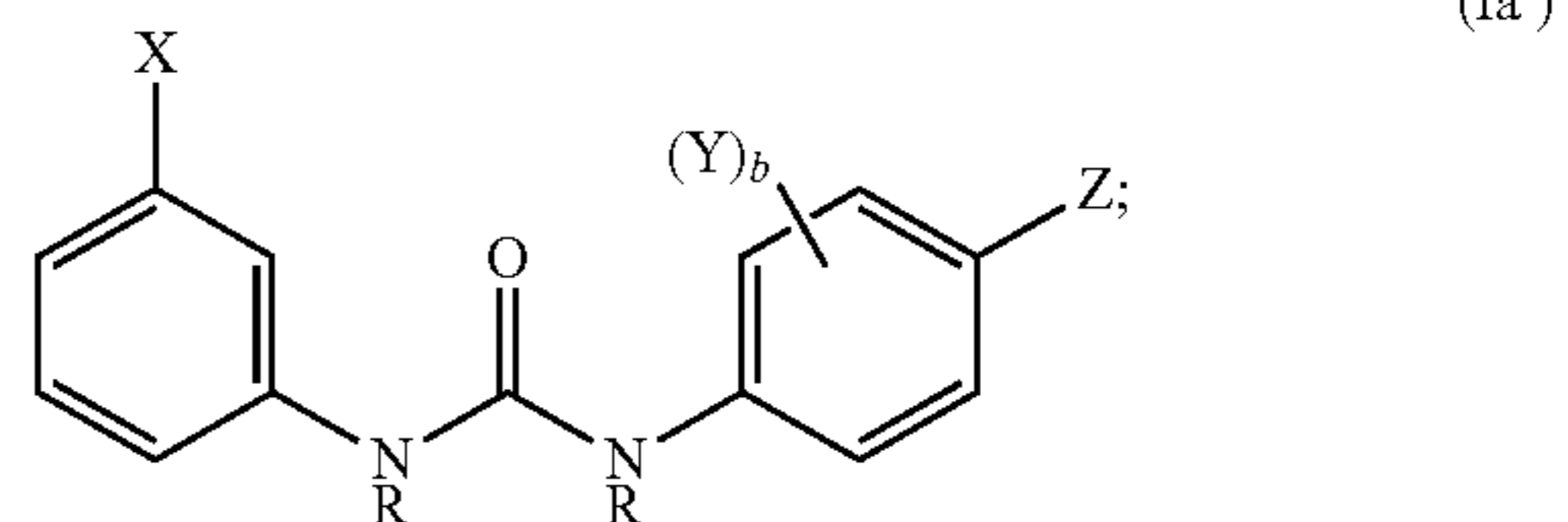
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or any pharmaceutically acceptable salt or solvate thereof.

In further embodiments, the compounds of the present disclosure include novel compounds represented by Formula (Ia') or (Ia'') or (Ia''') or (Ia''') or (Ia''') or one of (Ia⁶⁻¹⁰)

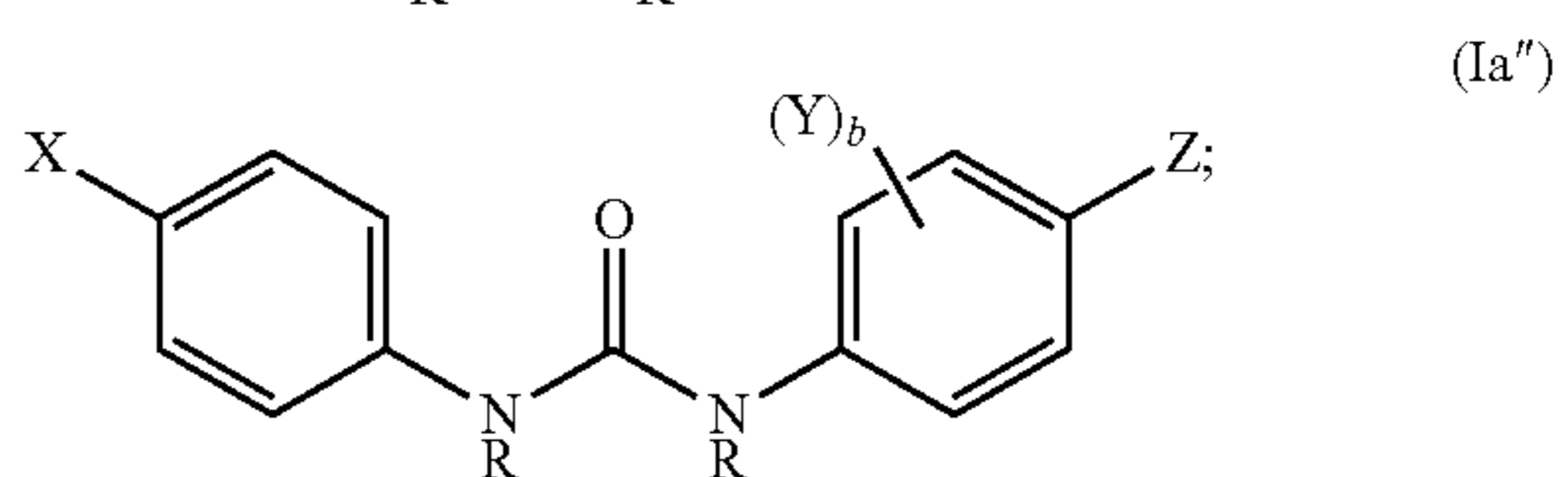
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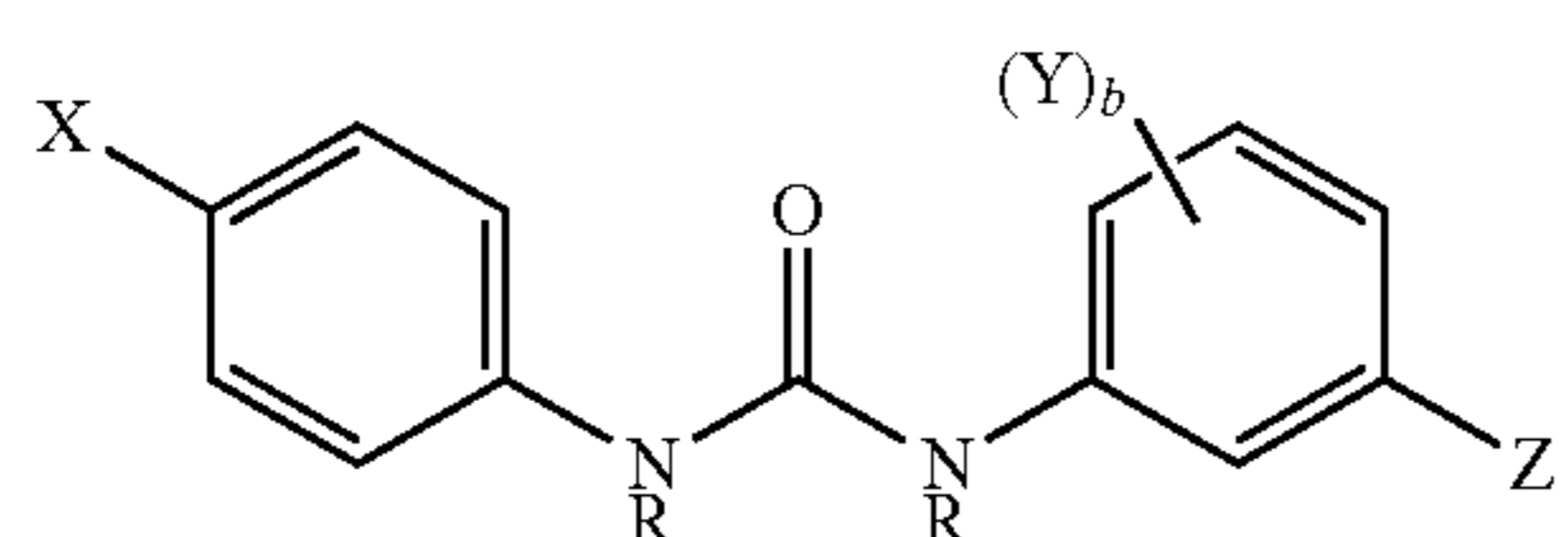
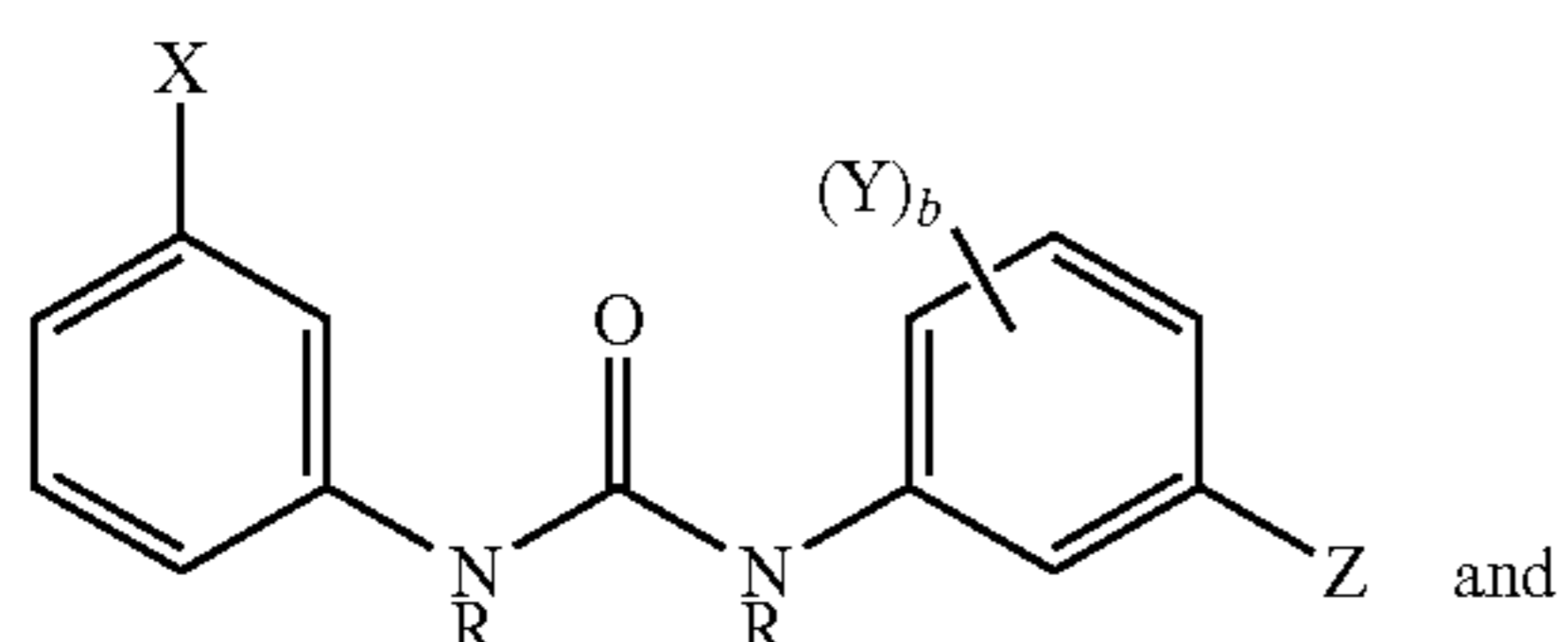
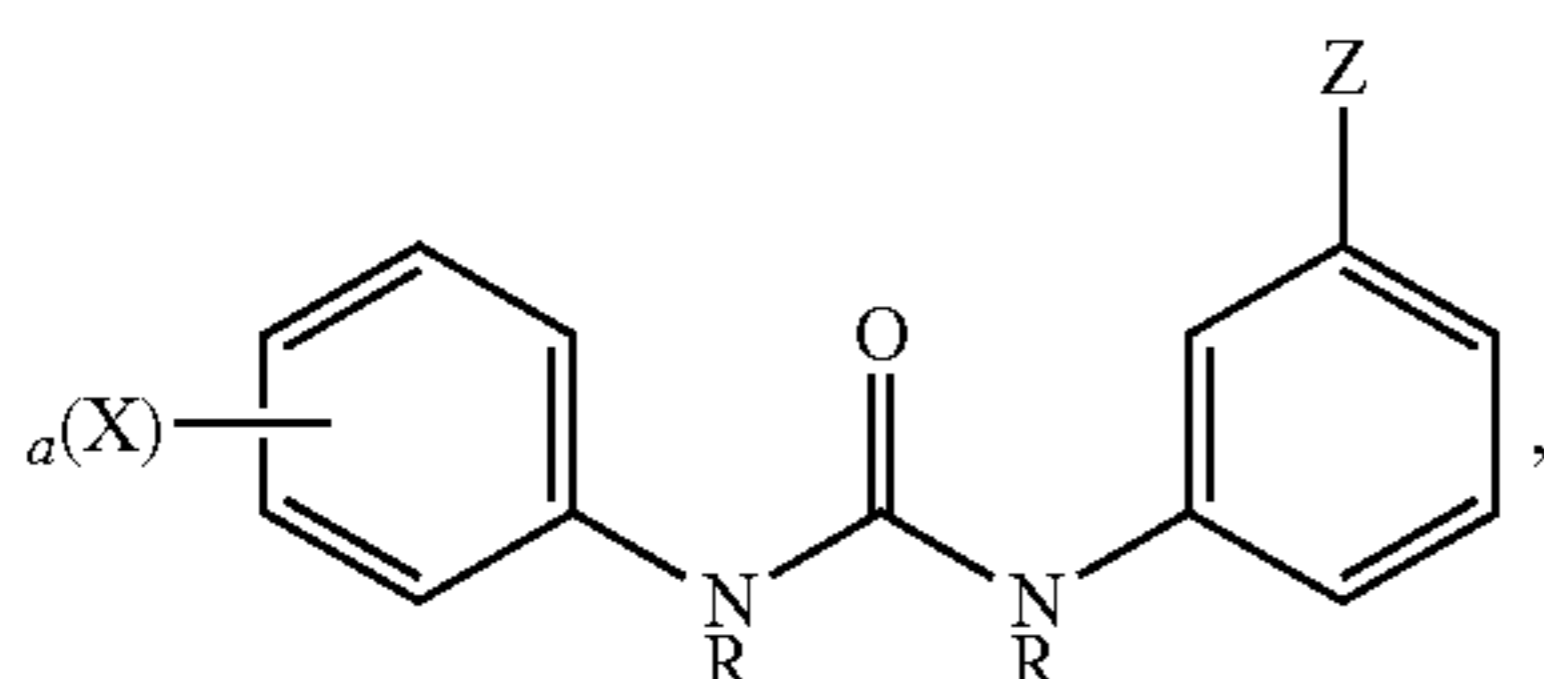
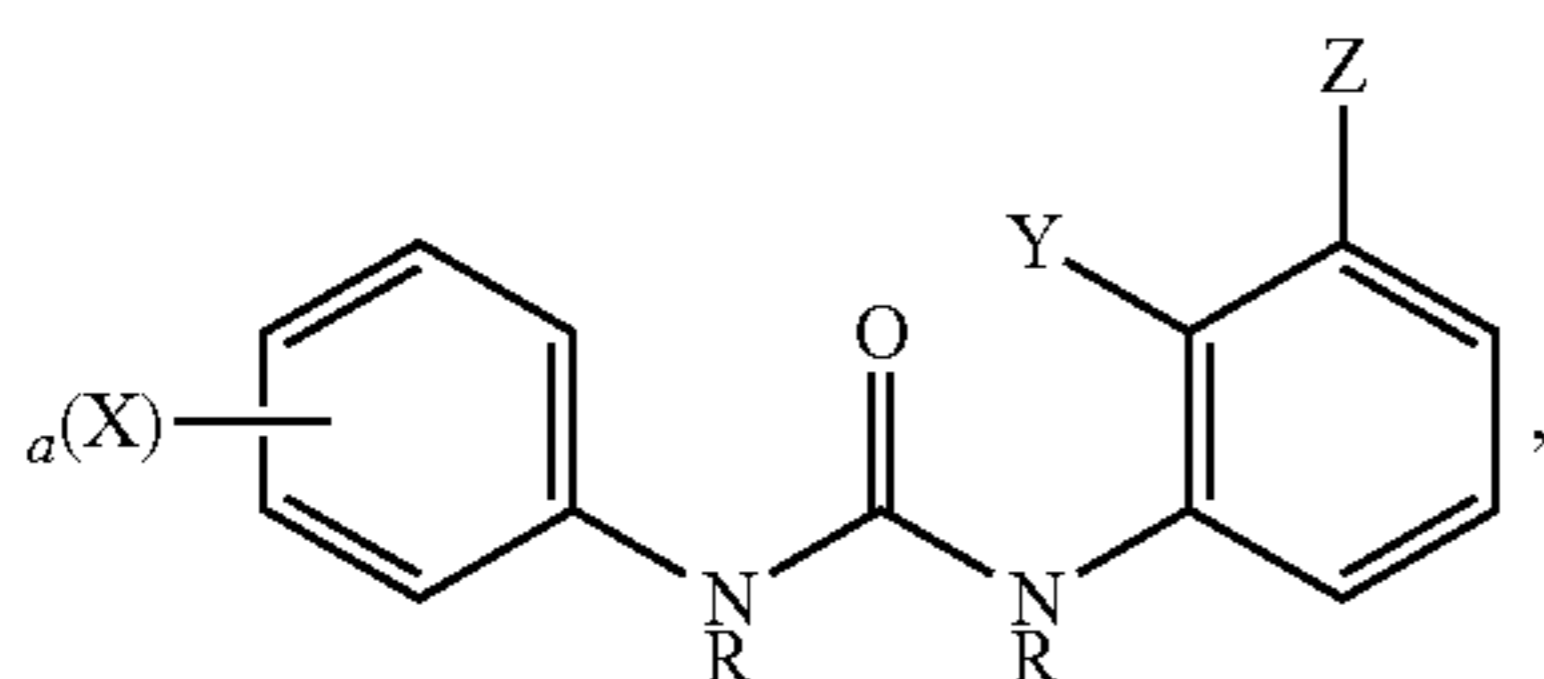
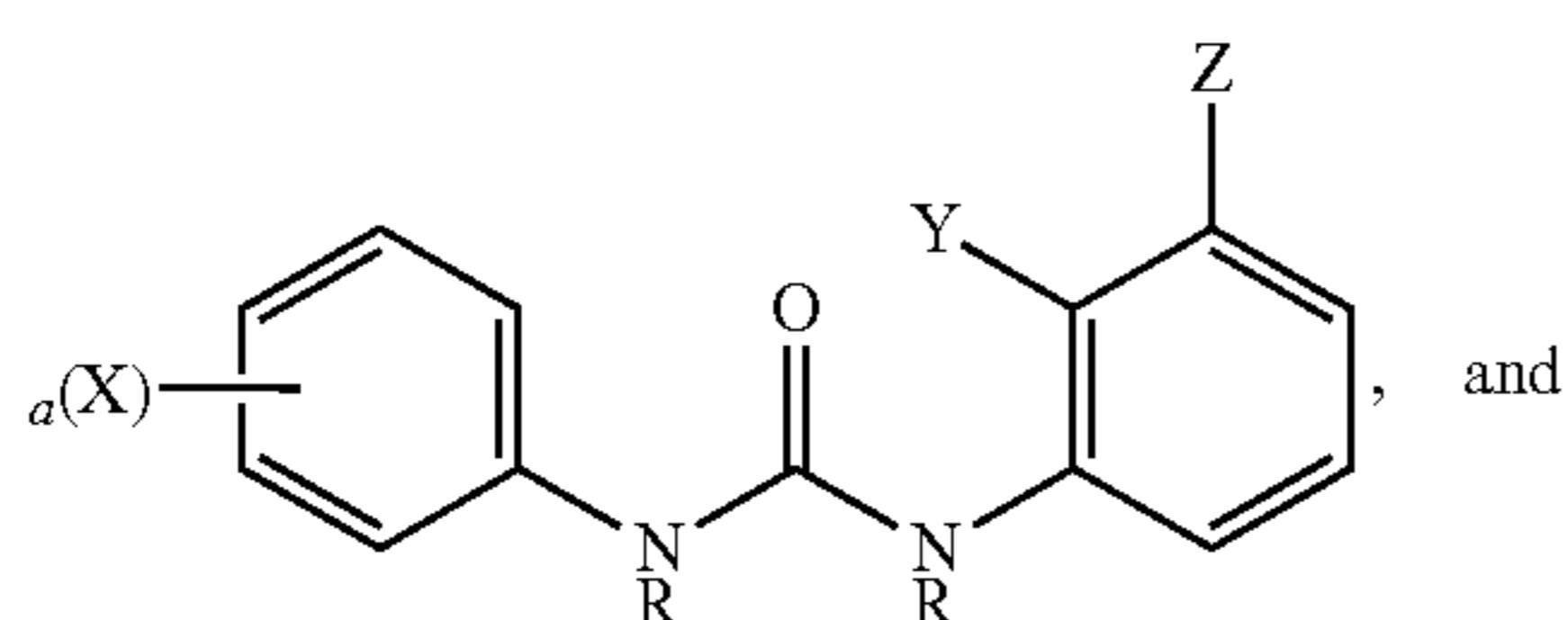
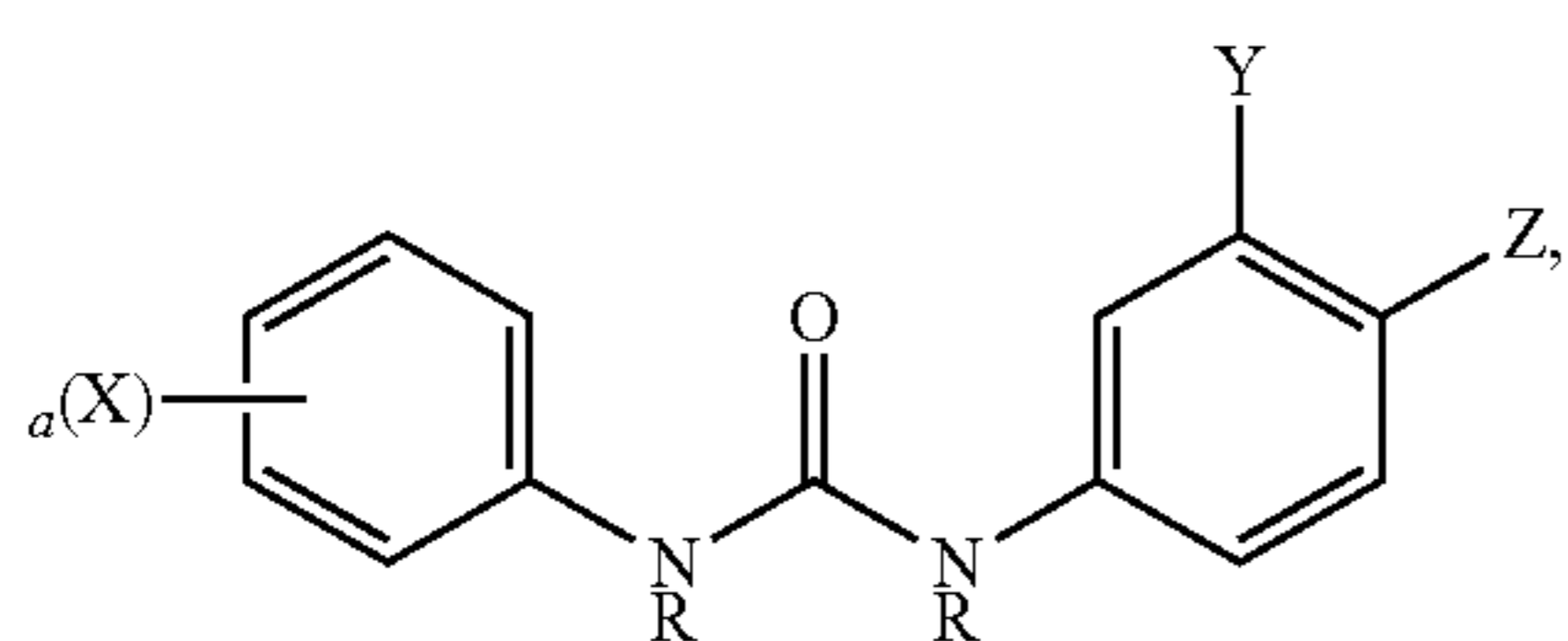
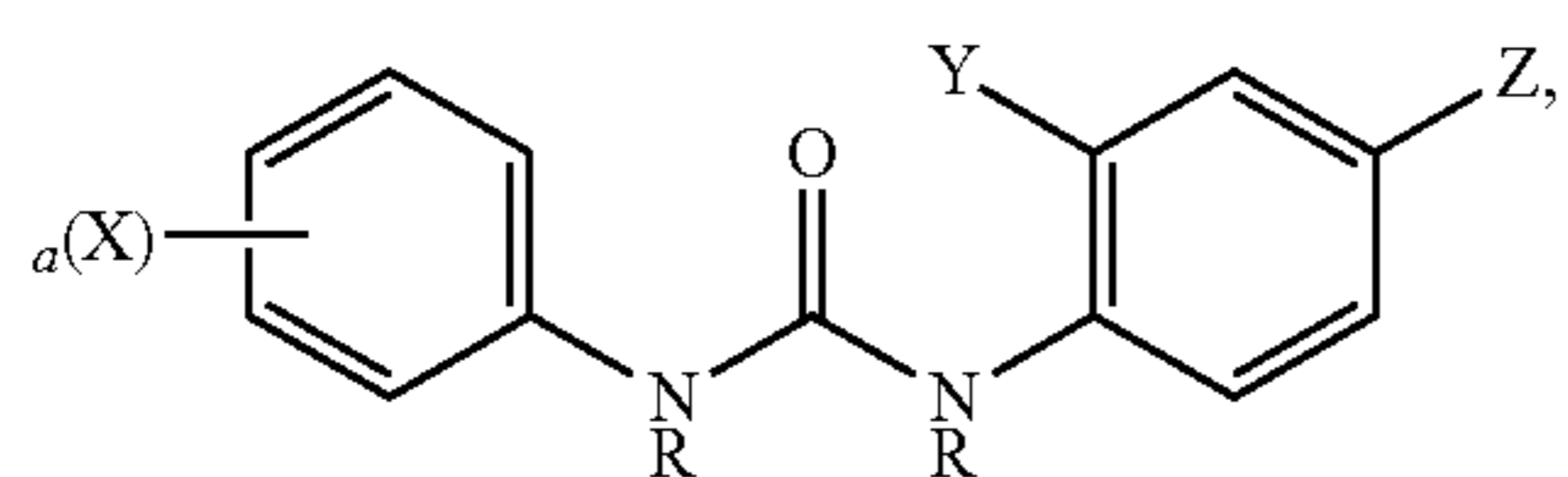
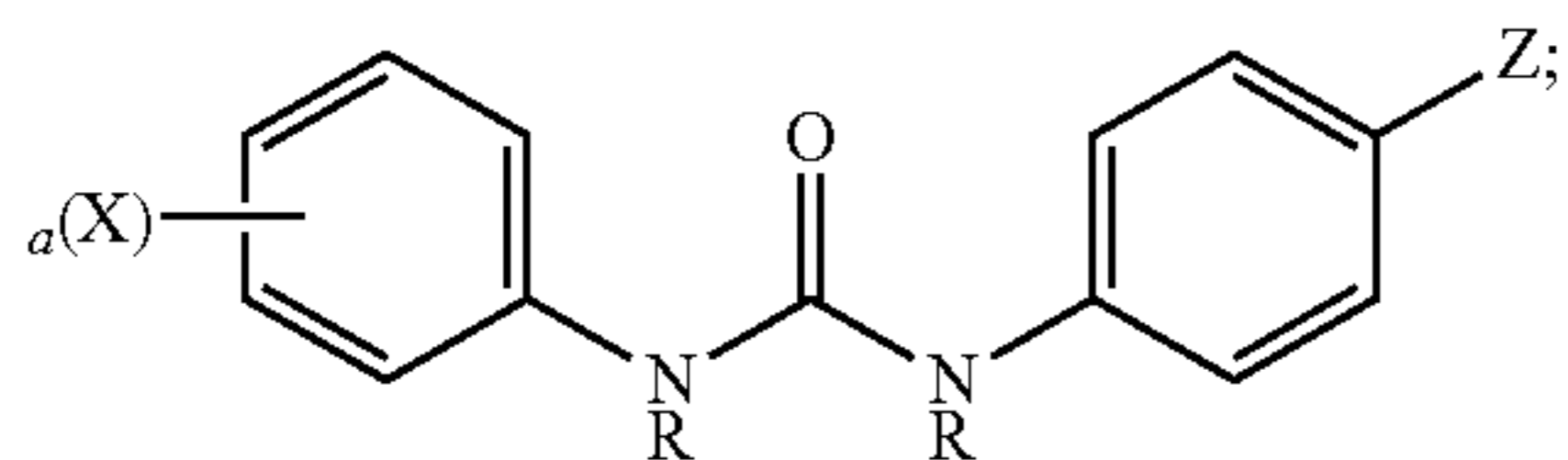
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or any pharmaceutically acceptable salt or solvate thereof.

The variables of formulae (Ia), (Ia'), (Ia''), (Ia'''), (Ia'''''), (Ia'''''''), and (Ia⁶⁻¹⁰) are the same as for Formula (I).

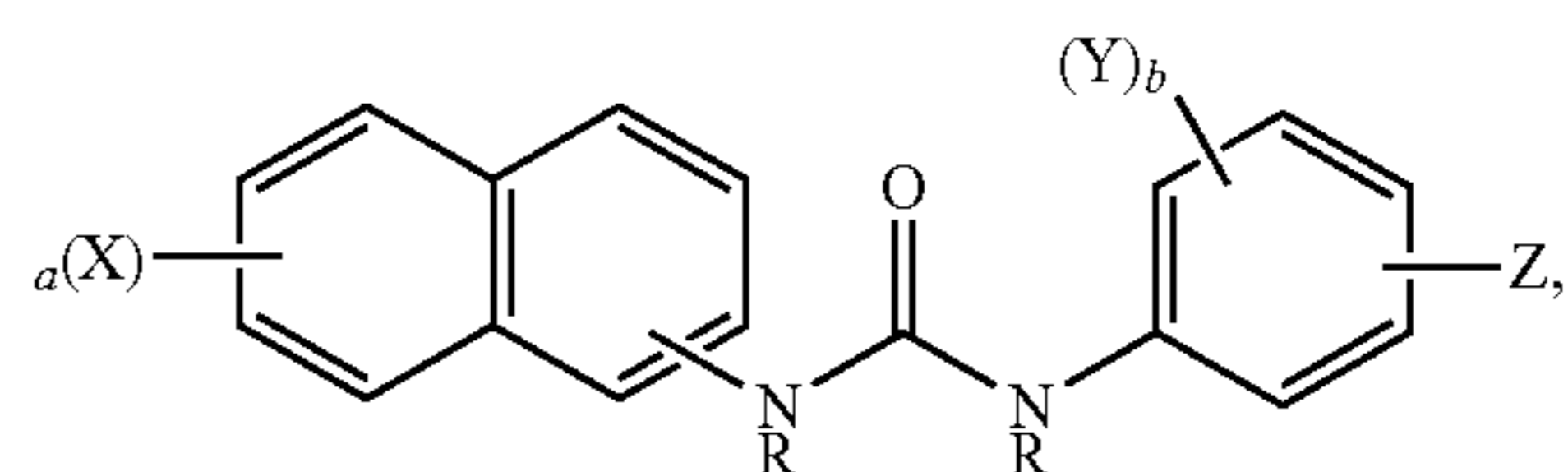
In some embodiments, when X in formula (Ia') is F, then Y is not methyl, and when X is Cl, then Y is not Cl, and in Formula (Ia''') when X is methyl and a is two, R is not in each instance H.

Other embodiments include compounds represented by Formula (Ib):

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(Ia''')

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(Ia''''')

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or any pharmaceutically acceptable salt or solvate thereof wherein the variables of Formula (Ib) are the same as for Formula (I).

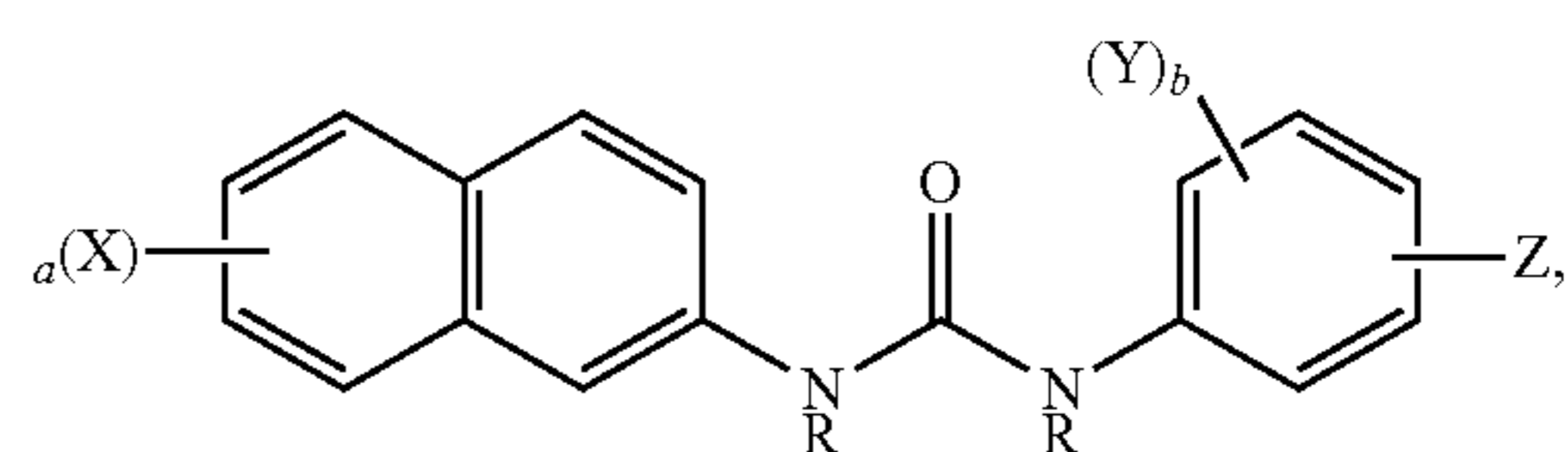
Some embodiments include compounds represented by Formula (Ib') and (Ib'')

(Ia''''''')

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(Ia⁶)

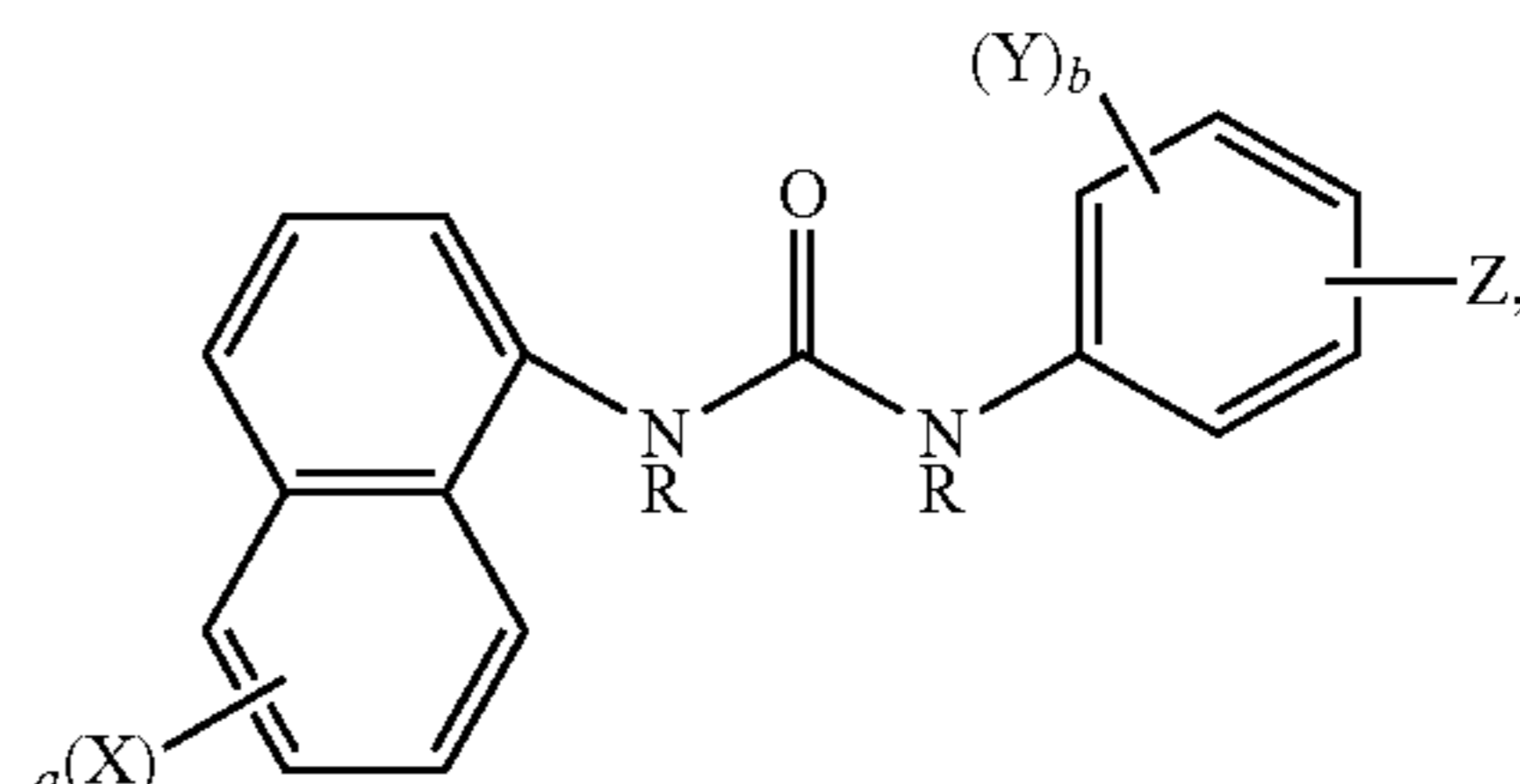
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(Ib')

(Ia⁷)

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(Ib'')

(Ia⁸)

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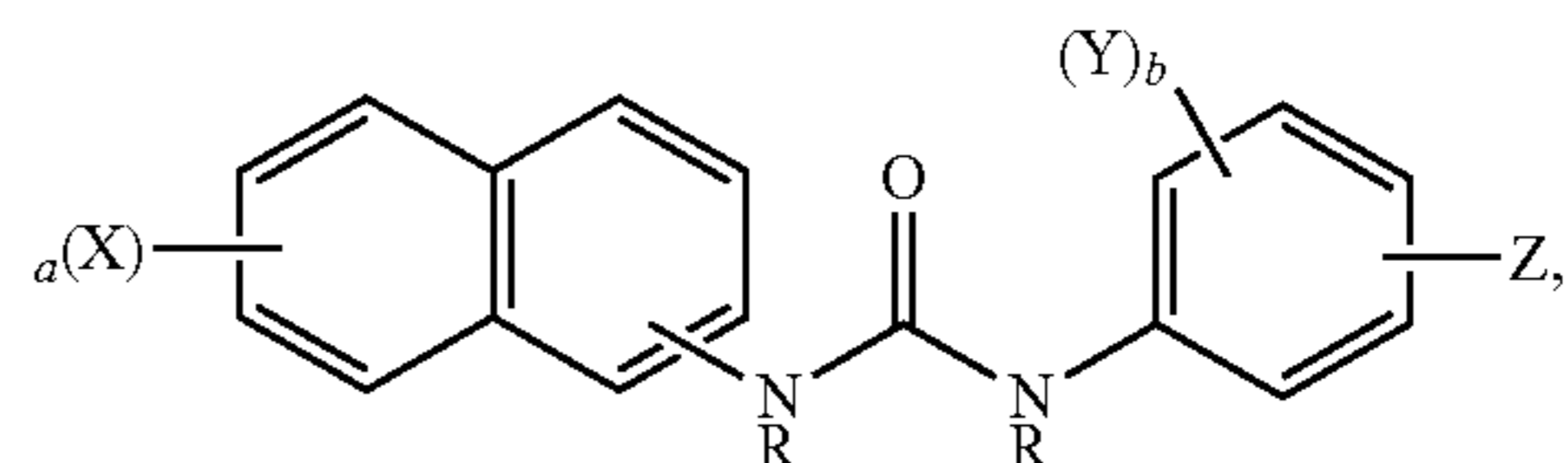
or any pharmaceutically acceptable salt or solvate thereof wherein the variables are the same as for Formula (I).

Other embodiments include compounds represented by Formula (Ib):

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(Ia⁹)

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(Ib)

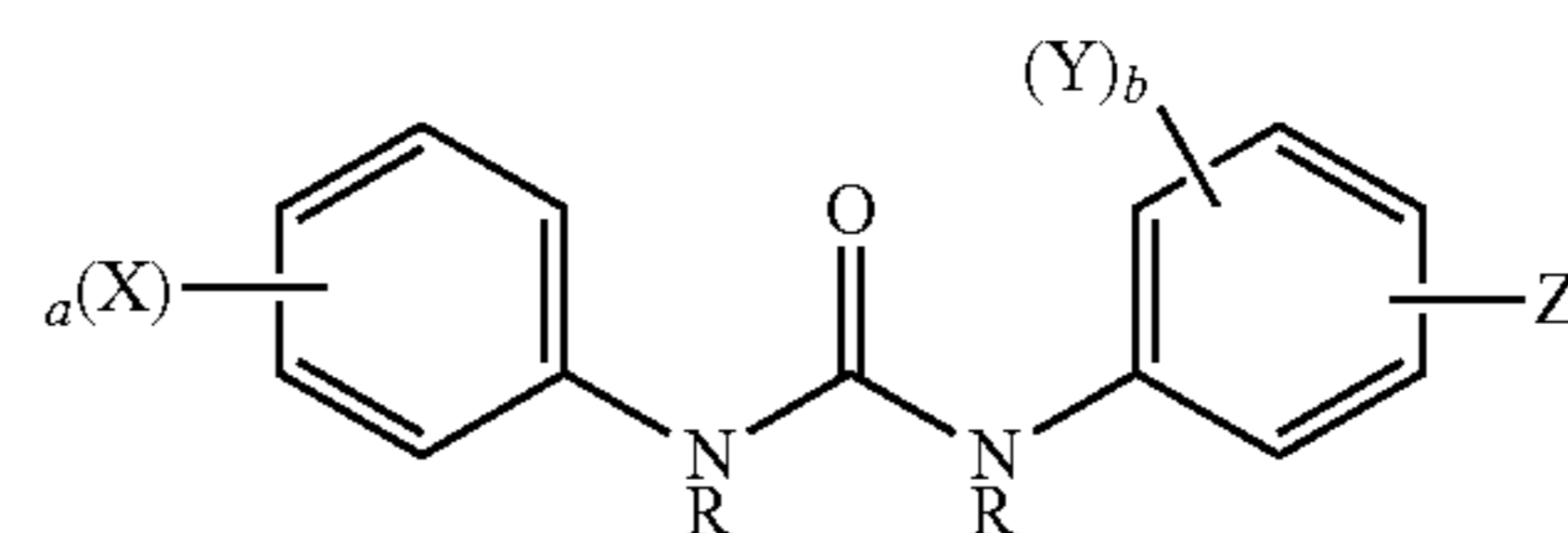
or any pharmaceutically acceptable salt or solvate thereof wherein the variables of Formula (Ib) are the same as for Formula (I).

In some embodiments, the compounds of the present disclosure include novel compounds represented by Formula (Ic):

(Ia¹⁰)

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(Ic)

or any pharmaceutically acceptable salt or solvate thereof, wherein two of X and/or two of Y are present on adjacent atoms, and together form a five or six-membered aryl, heteroaryl, heterocyclic or cyclic ring that is optionally substituted by one or more halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆

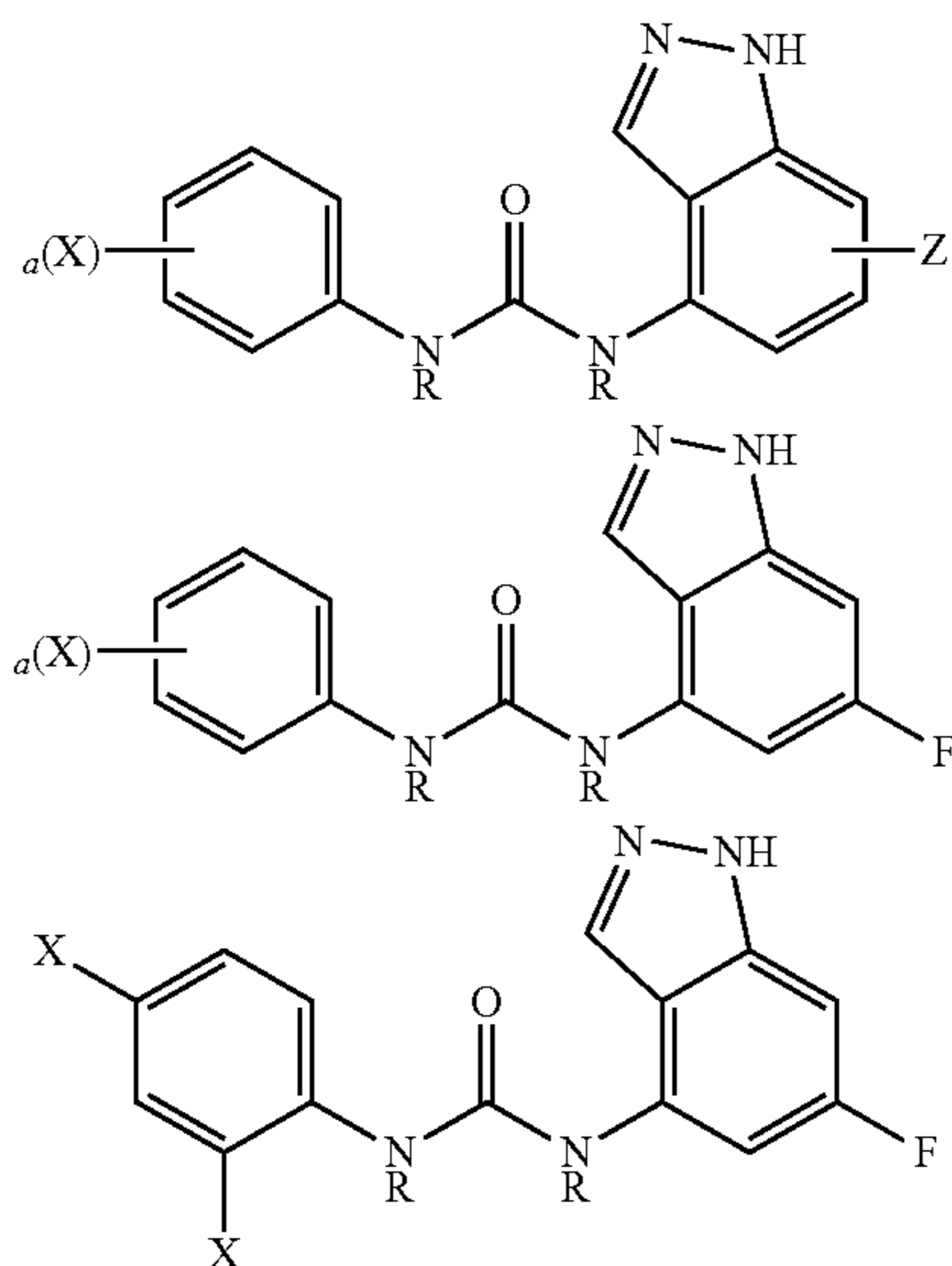
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perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₆)arylene, and the remaining variables of Formula (Ic) are the same as for Formula (I).

In some embodiments, the two of X and/or two of Y are present on adjacent atoms, and together form a five or six-membered aryl ring. In some embodiments, the two of X and/or two of Y are present on adjacent atoms, and together form a five or six-membered heteroaryl ring. In some embodiments, the two of X and/or two of Y are present on adjacent atoms, and together form a five or six-membered heterocyclic ring. In some embodiments, the two of X and/or two of Y are present on adjacent atoms, and together form a five or six-membered cyclic ring. In some embodiments, the heteroatom is N. In some embodiments, the heteroatom is O. In some embodiments, the heterocycle/heteroaryl is selected from pyrrole, 1-pyrroline, 2-pyrroline, 3-pyrroline, pyrrolidone, imidazole, imidazoline, imidazolidine, pyrazole, 2-pyrazoline, 3-pyrazoline, pyrazolidine, 1,3,4-triazole, 1,2,3-triazole, 1,2,4-triazole, tetrazole, pentazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, 1,4-dihydropyridine, dihydropyrazine, piperidine, and piperazine.

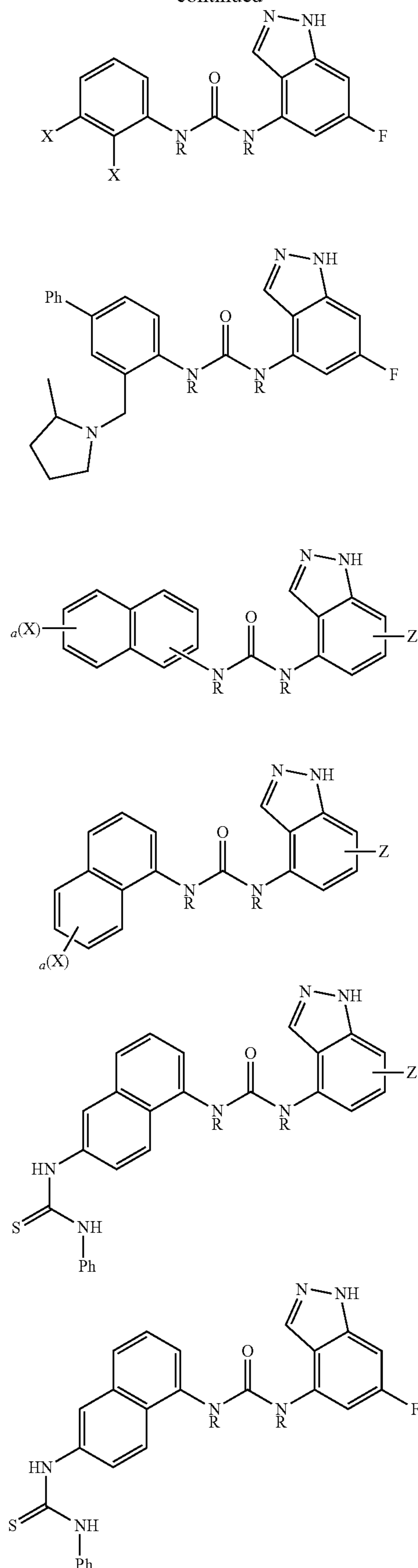
In some embodiments, the two X are present on adjacent atoms, and together form a five or six-membered aryl or heteroaryl or heterocyclic or cyclic ring. In some embodiments, the two Y are present on adjacent atoms, and together form a five or six-membered aryl or heteroaryl or heterocyclic or cyclic ring. In some embodiments, the two X and the two Y are present on adjacent atoms, and each set together, independently, form a five or six-membered aryl or heteroaryl or heterocyclic or cyclic ring.

Compounds of Formula (Ic) include:



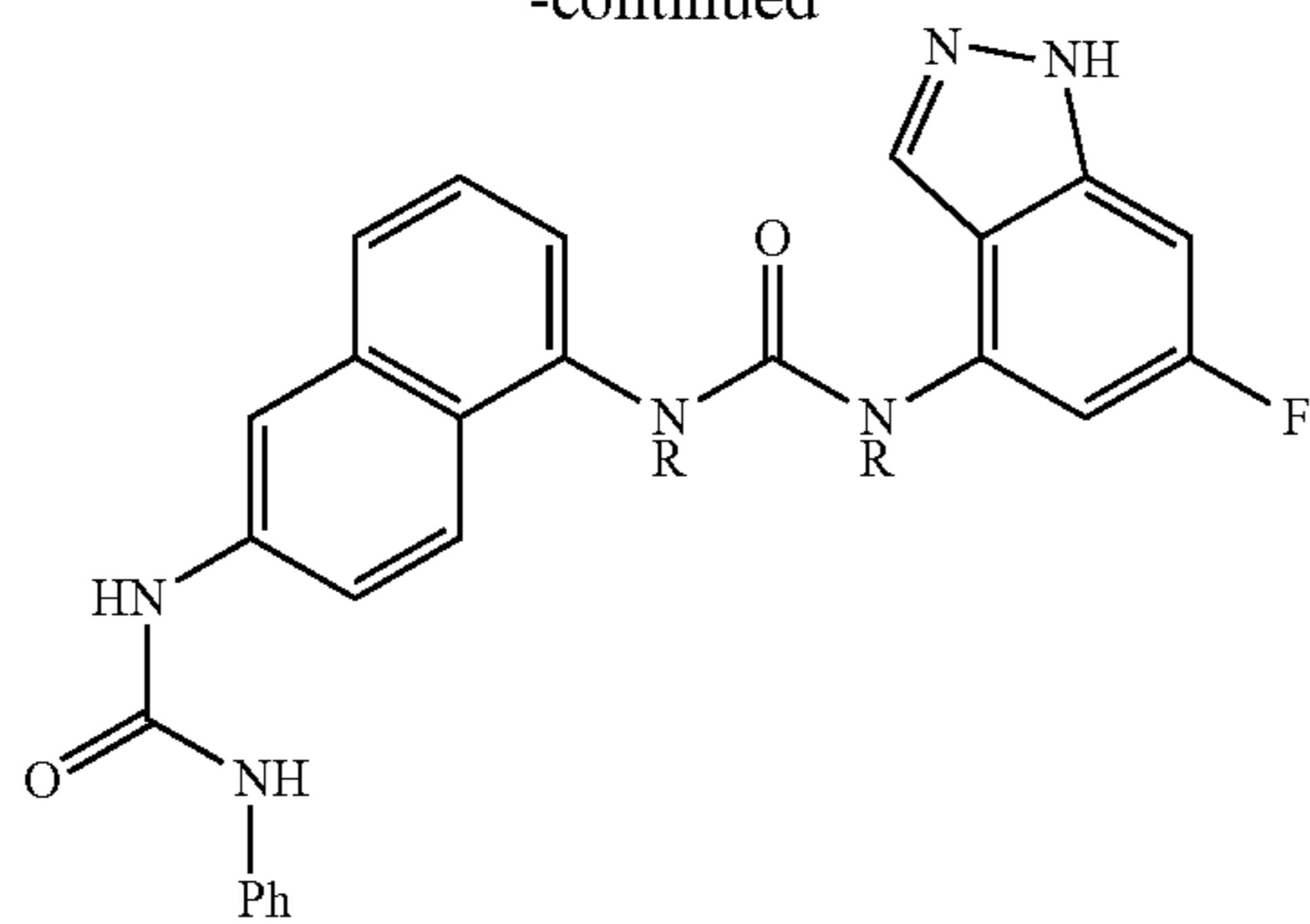
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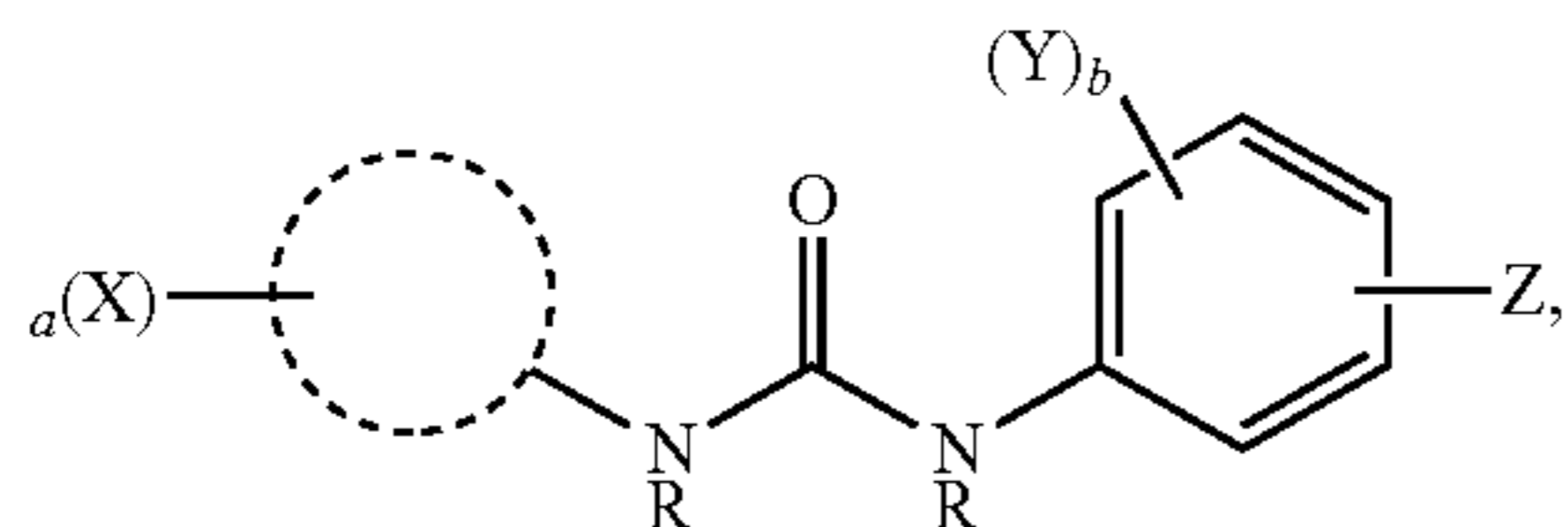
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In some of the above embodiments, each R is H. In some embodiments, each Z is F.

In some embodiments, the compounds of the present disclosure include novel compounds represented by Formula (Id):

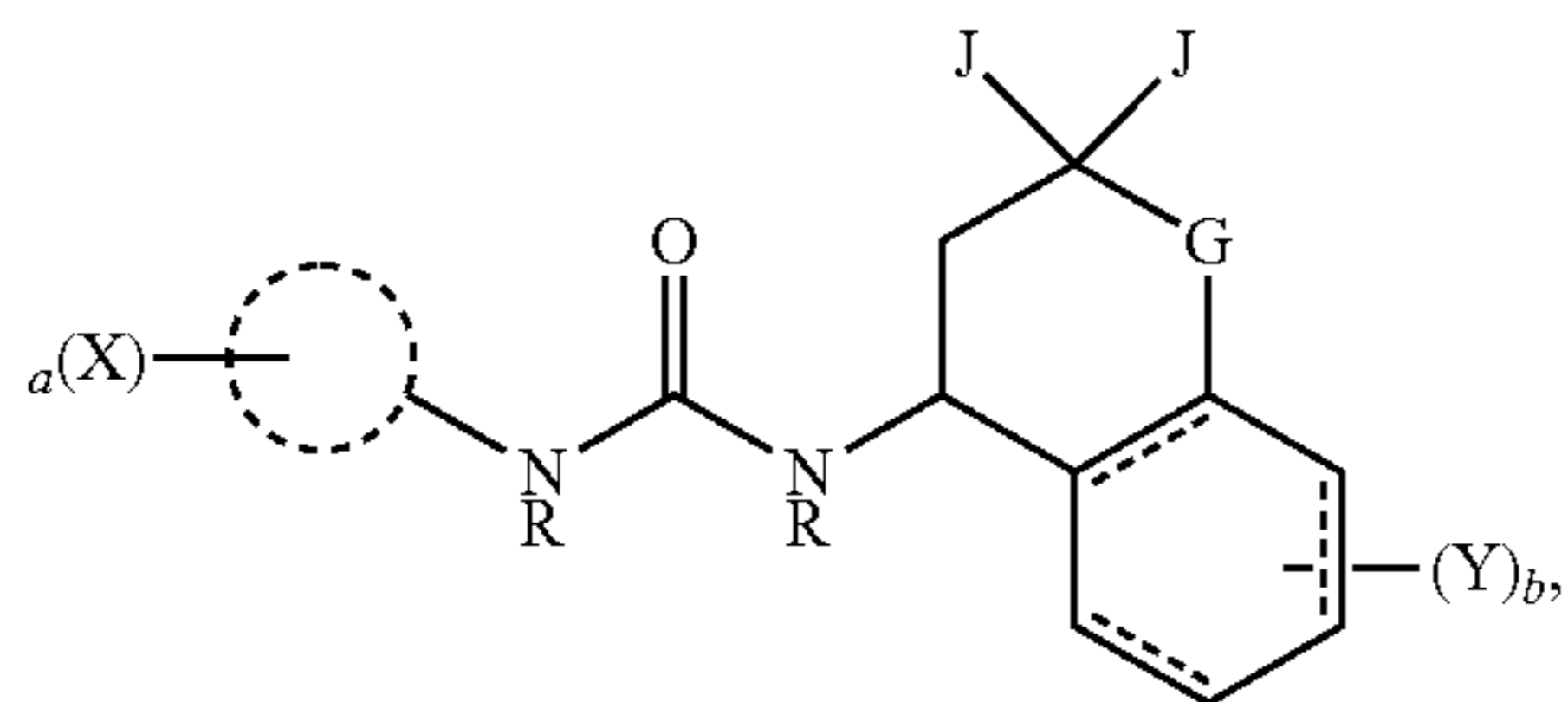


or any pharmaceutically acceptable salt or solvate thereof, wherein



is a 6- or 10-membered aryl (e.g., phenyl or naphthyl), and the variables of Formula (Id) are the same as for Formula (I) or (Ic).

In some embodiments, the compounds of the present disclosure include novel compounds represented by Formula (Ie):



or any pharmaceutically acceptable salt or solvate thereof, wherein



is a 6- or 10-membered aryl (e.g., phenyl or naphthyl);

--- represents an optional bond;

J is independently a C₁-C₆ alkyl substituted by one or more halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-

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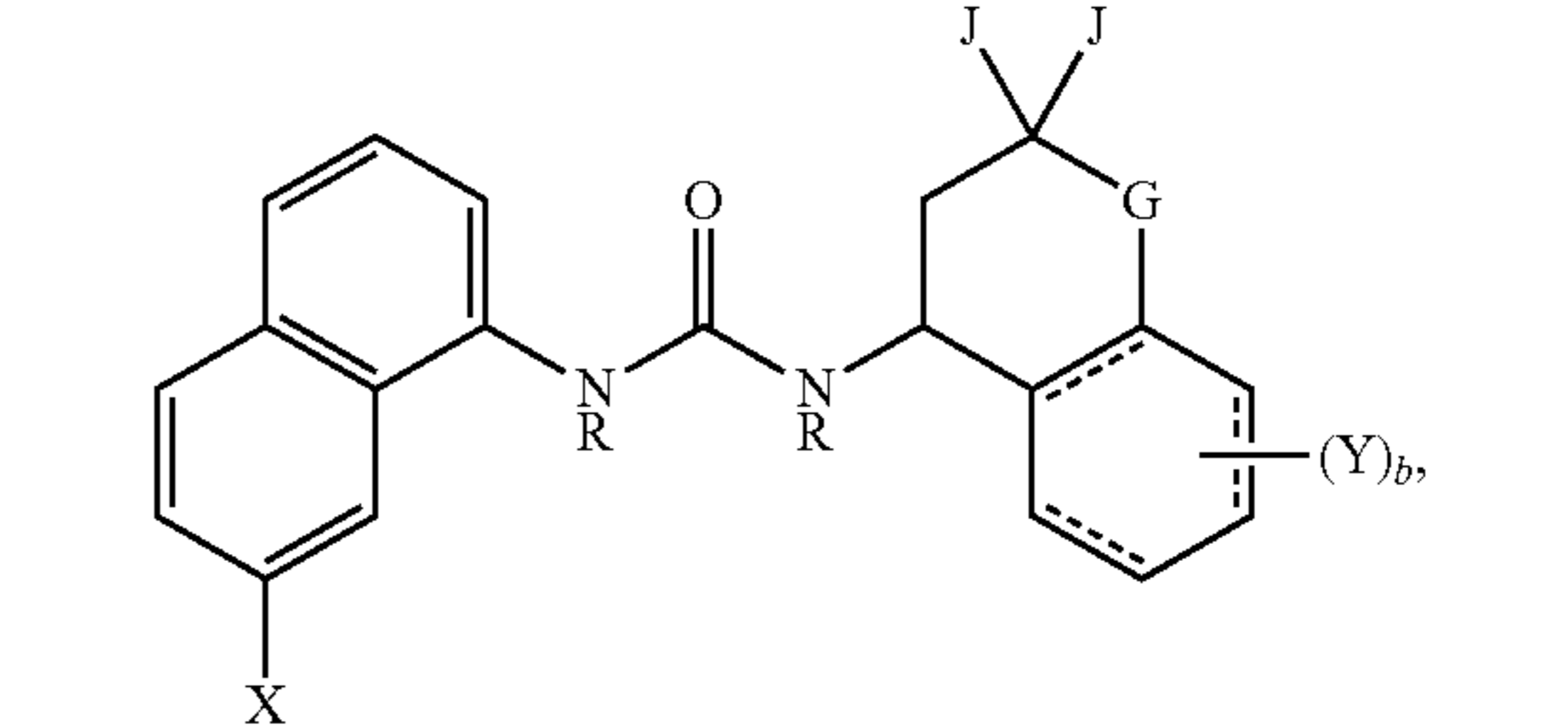
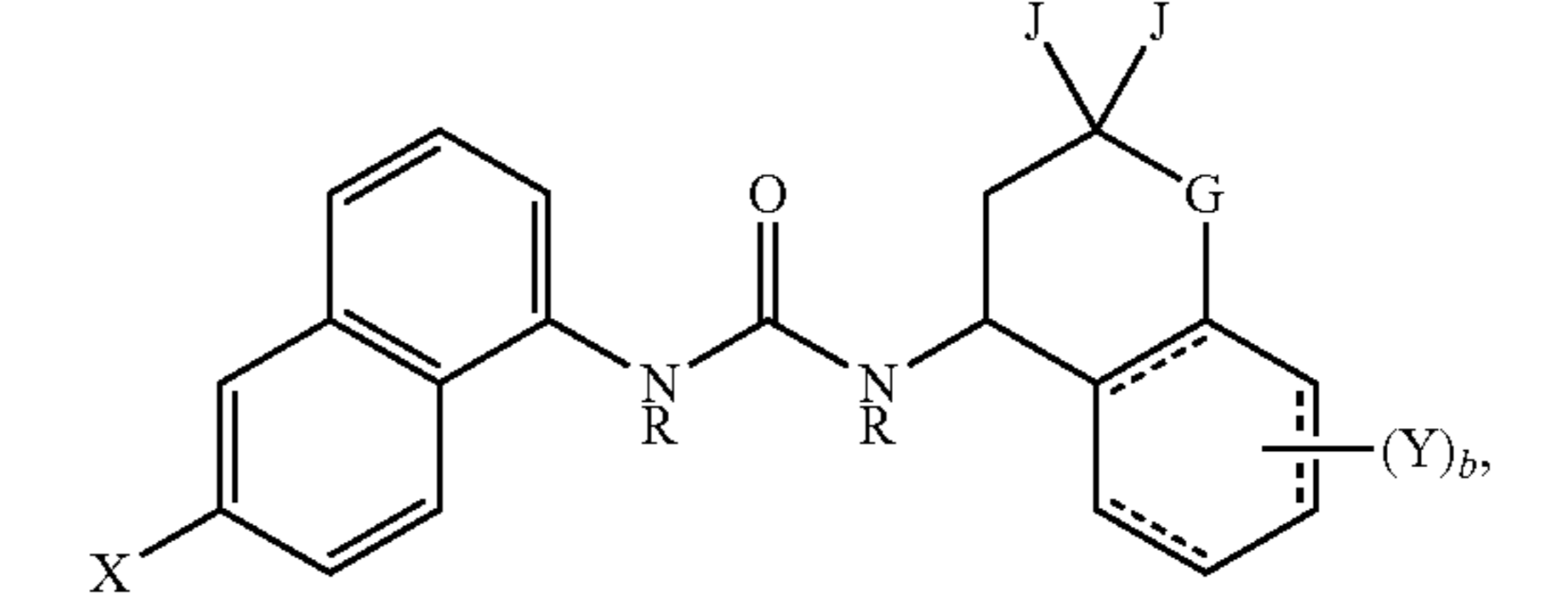
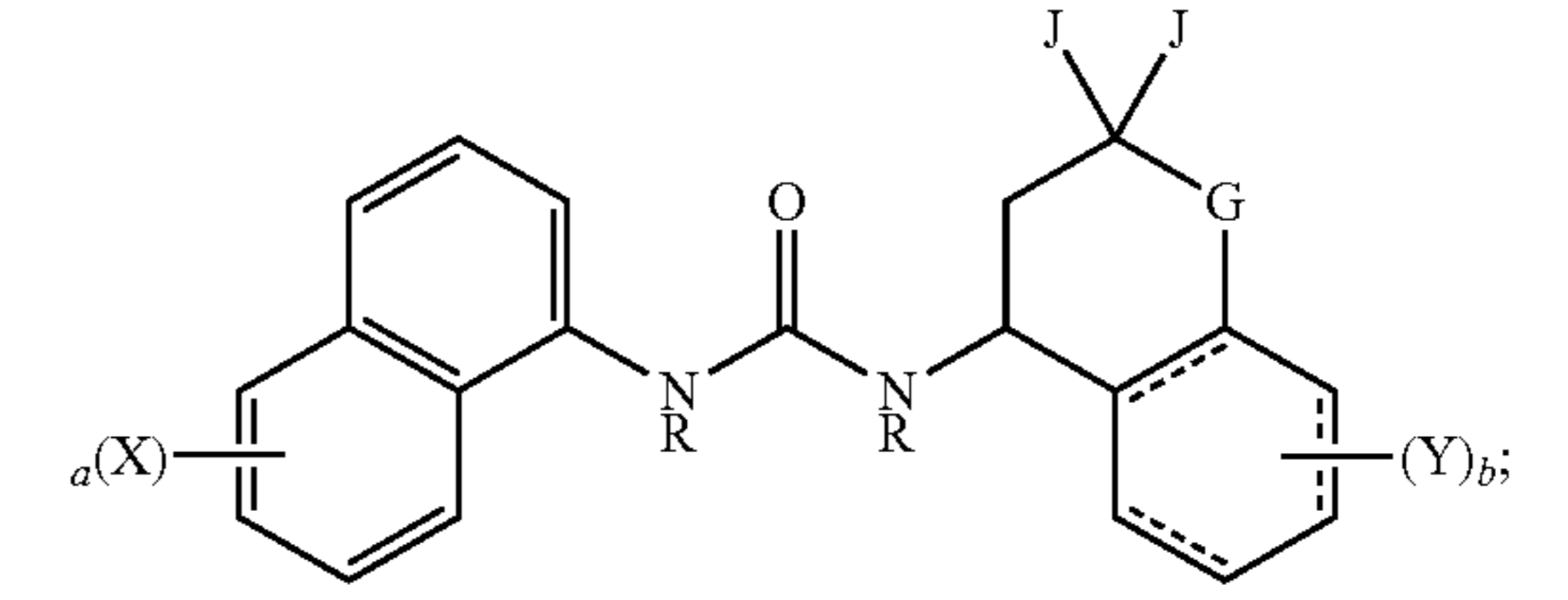
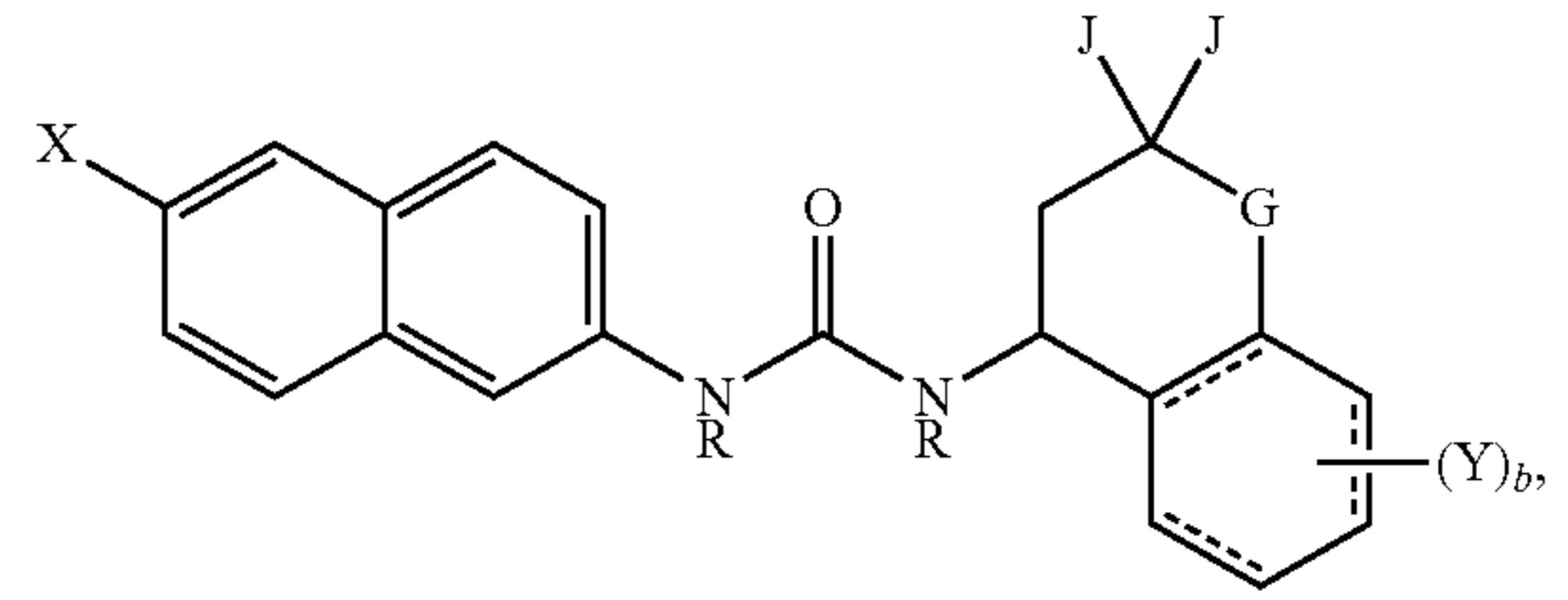
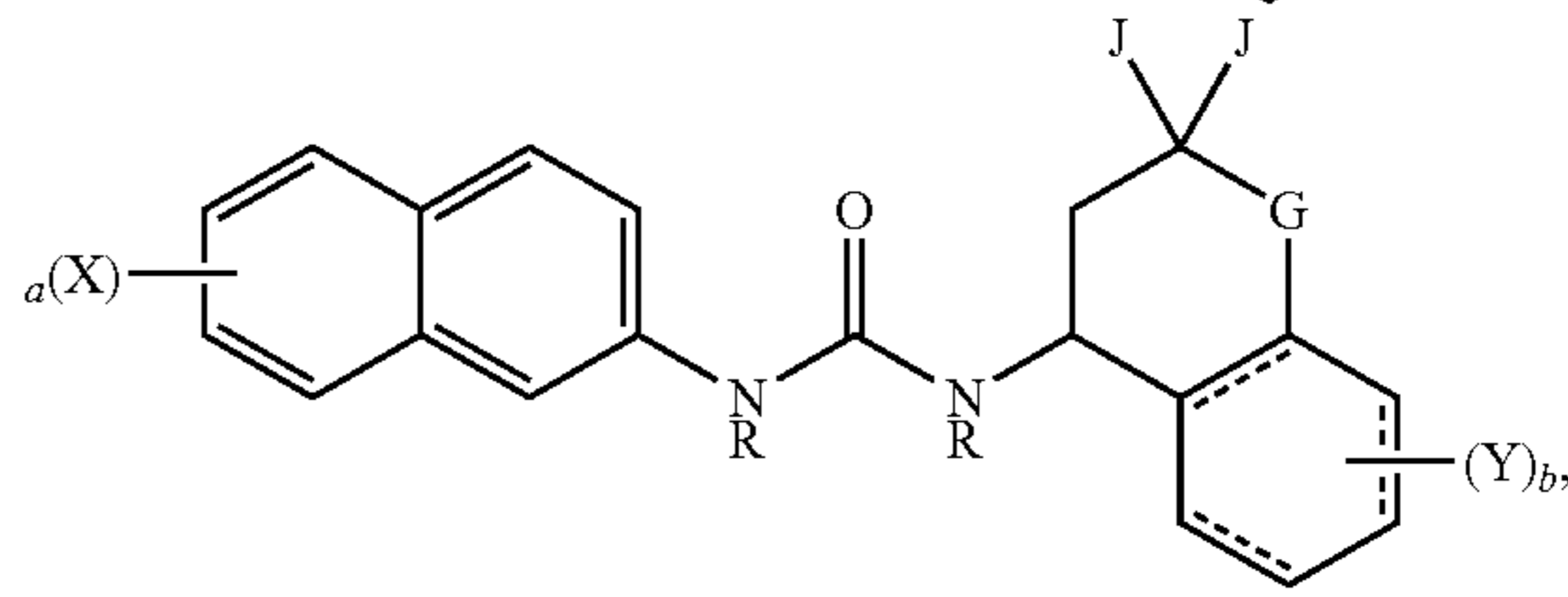
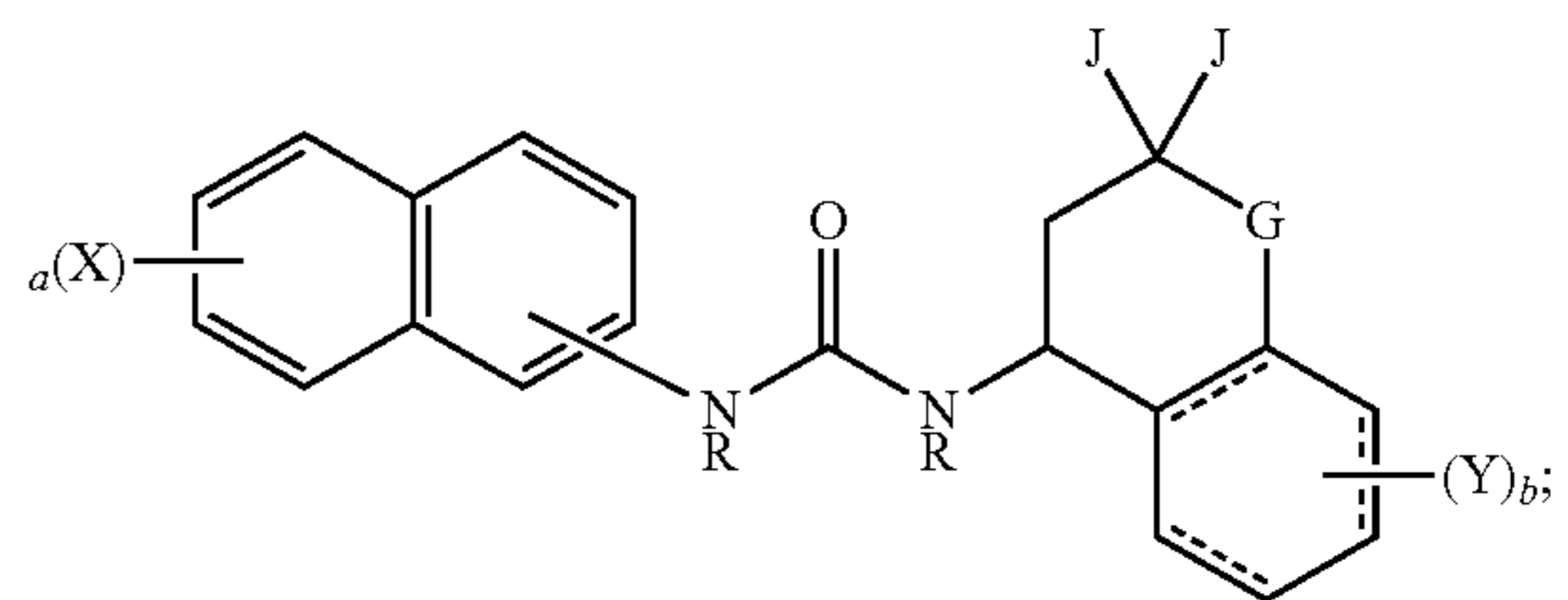
C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₆)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl-(C₁-C₆)alkylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene; G is CR₂, O, or NR;

and the variables of Formula (Ie) are the same as for Formula (I).

In some embodiments, J is selected from C₁-C₆-alkyl-halogen (e.g., Cl or F), C₁-C₆-alkyl-hydroxyl, and C₁-C₆ perfluoroalkyl.

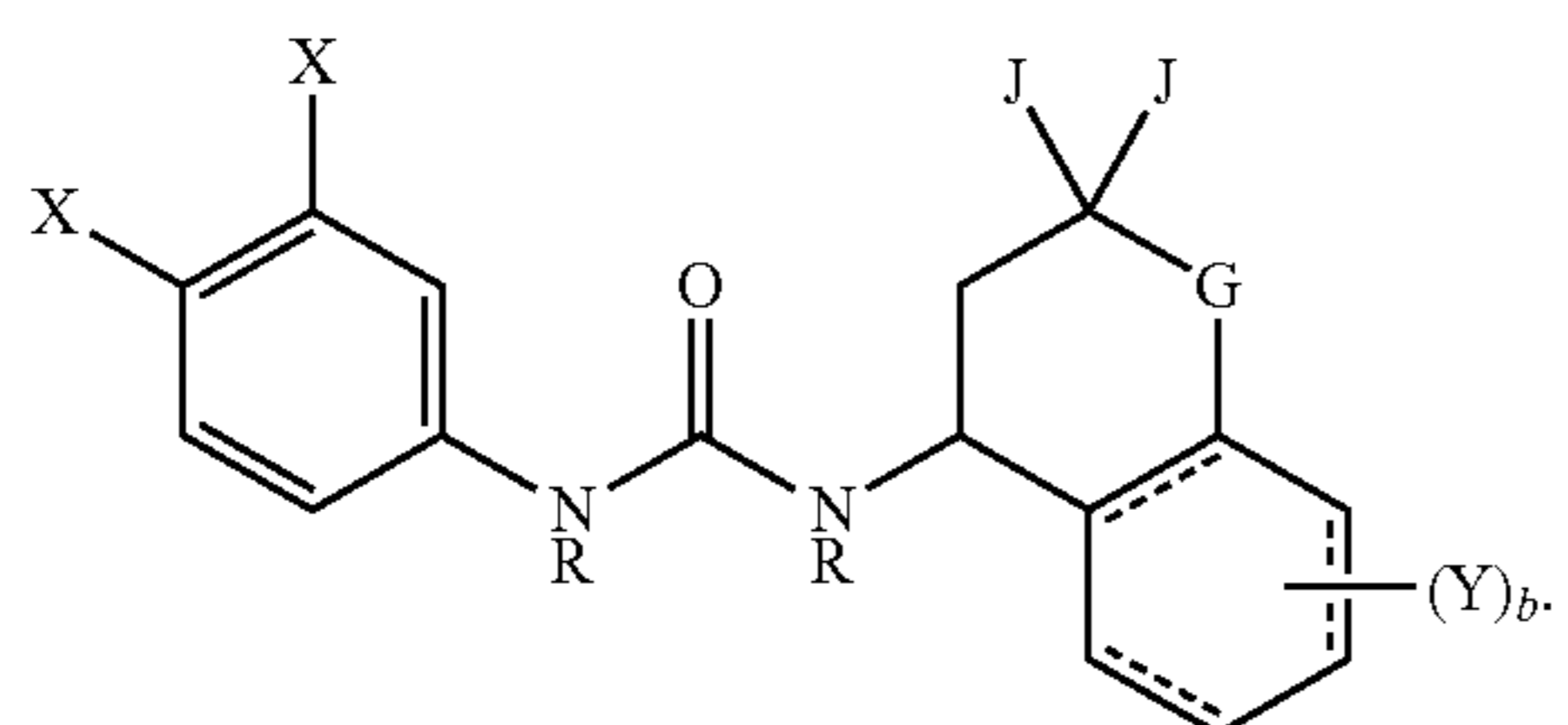
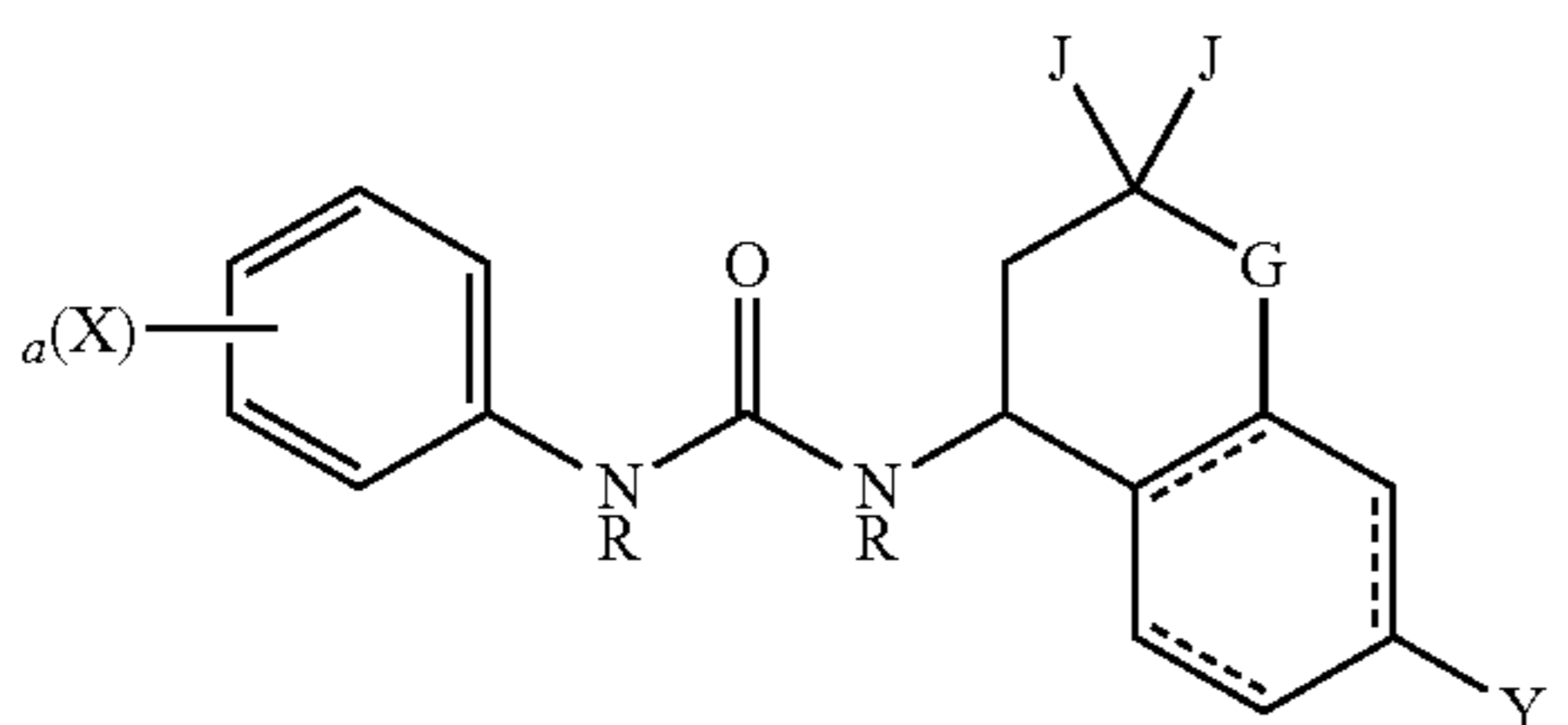
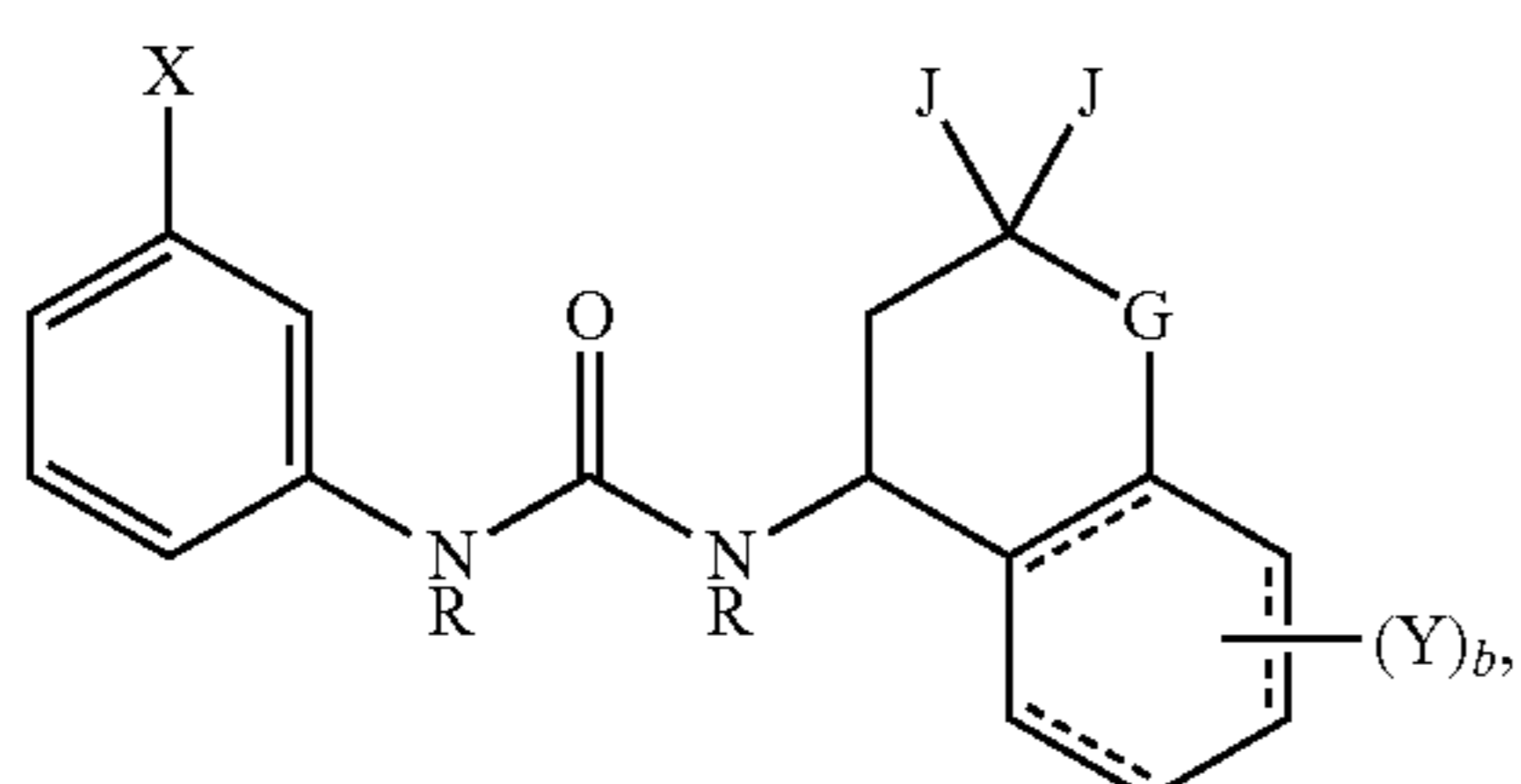
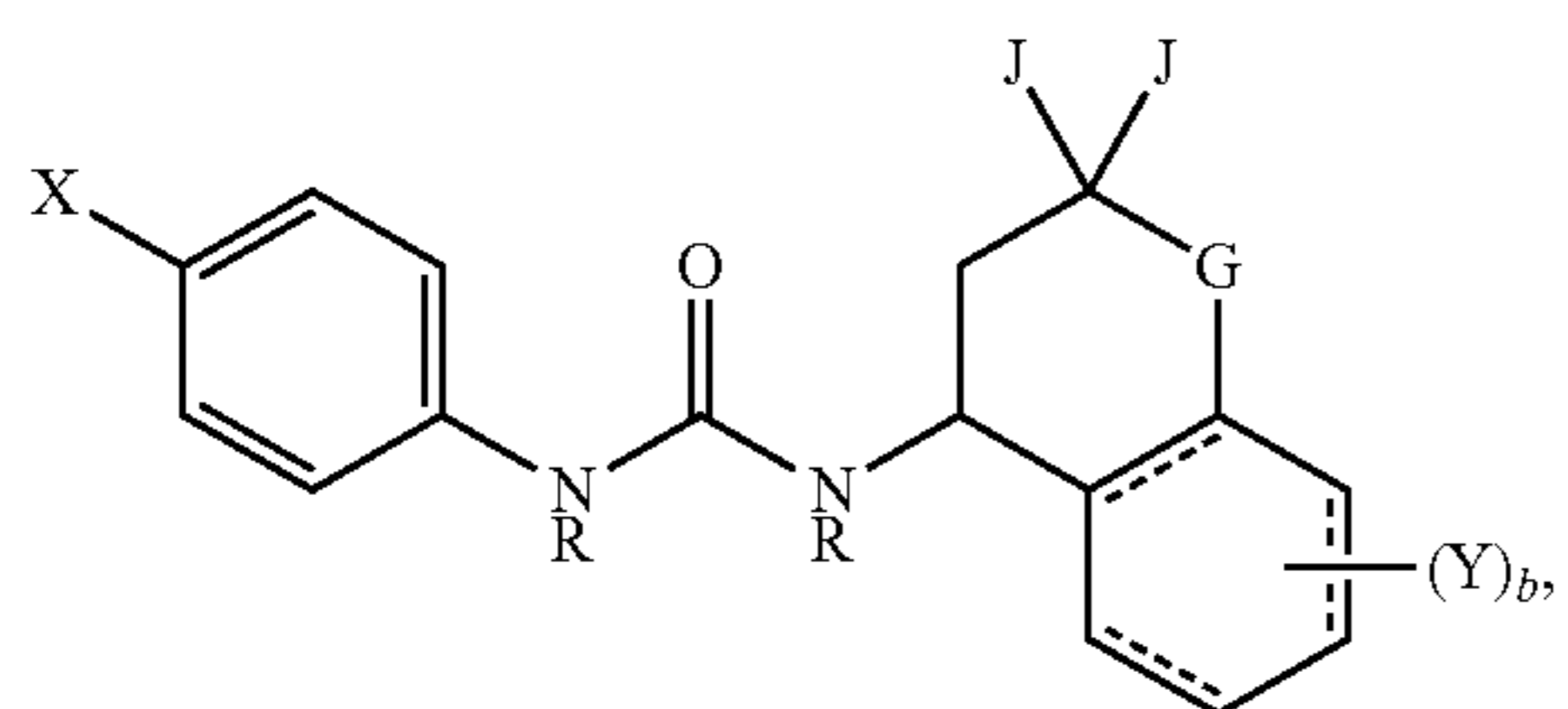
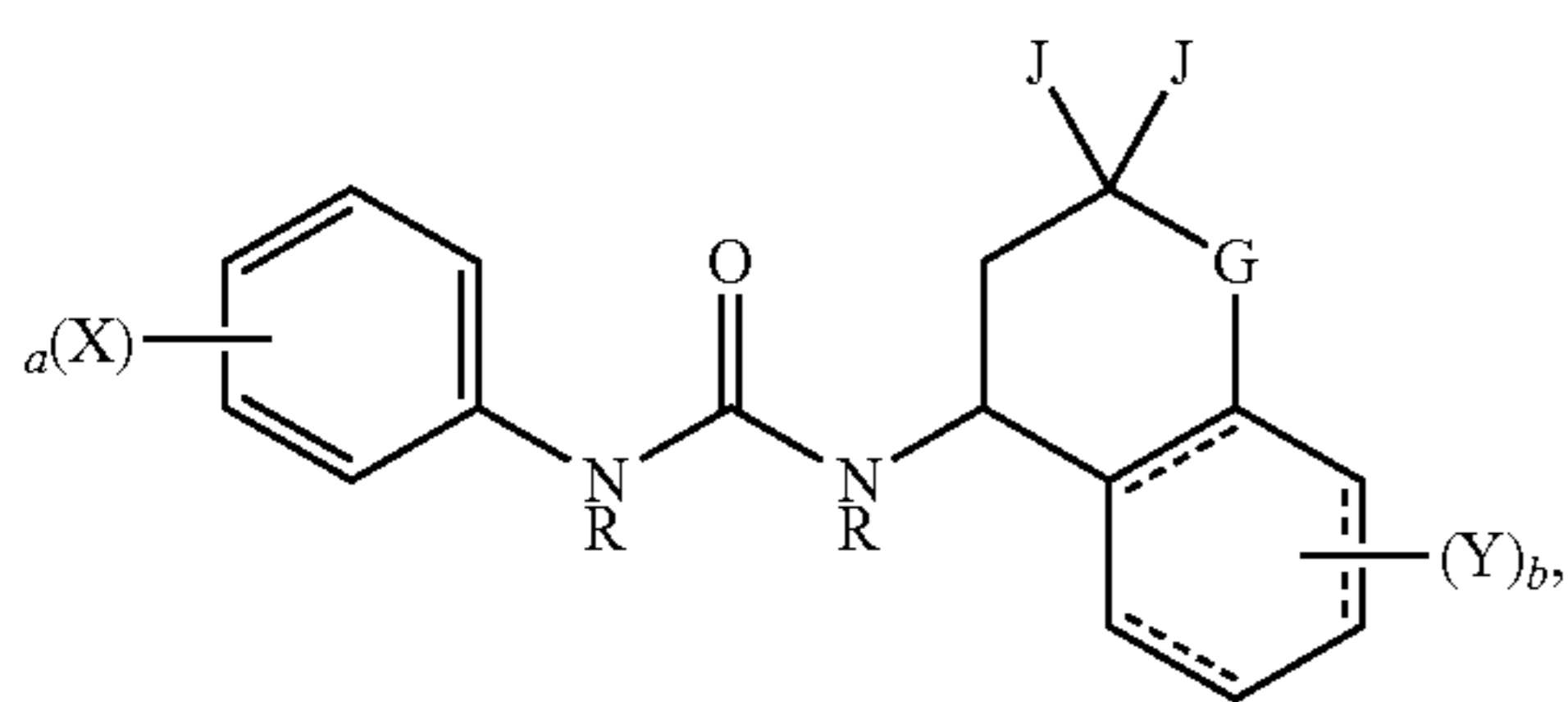
In some embodiments, G is O. In some embodiments, each of --- is present.

Additional embodiments of Formulae (Ie) include:

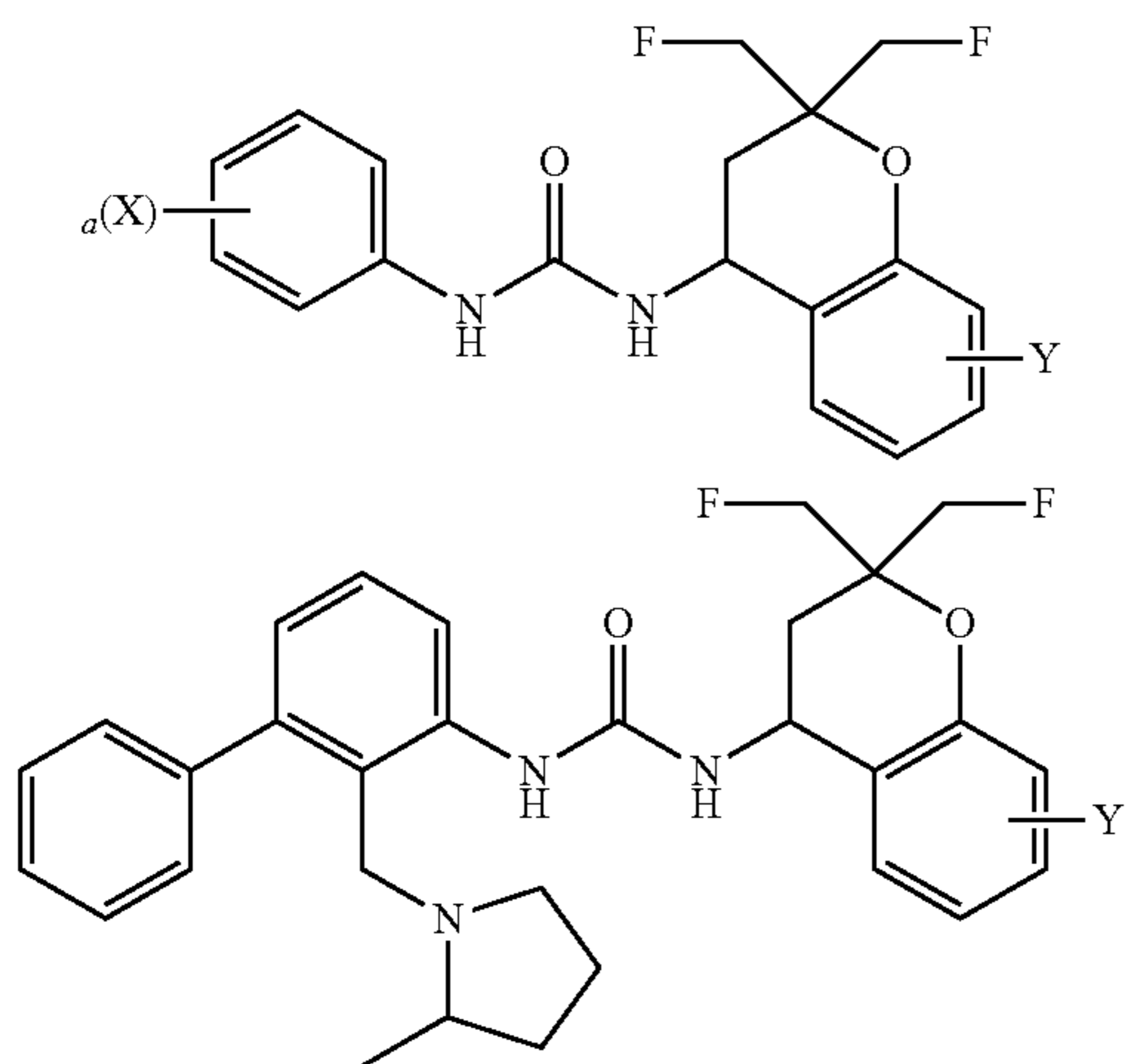


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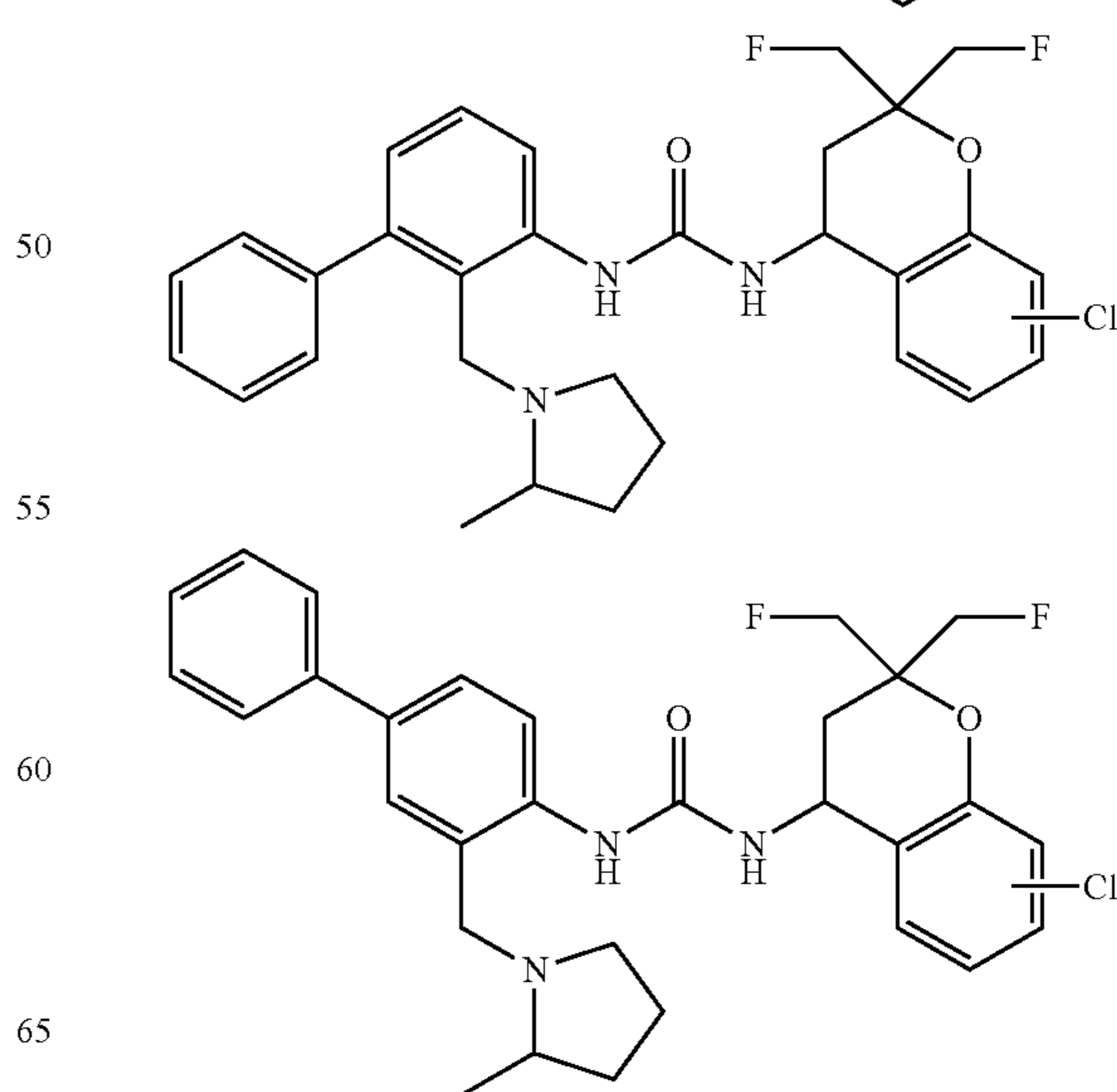
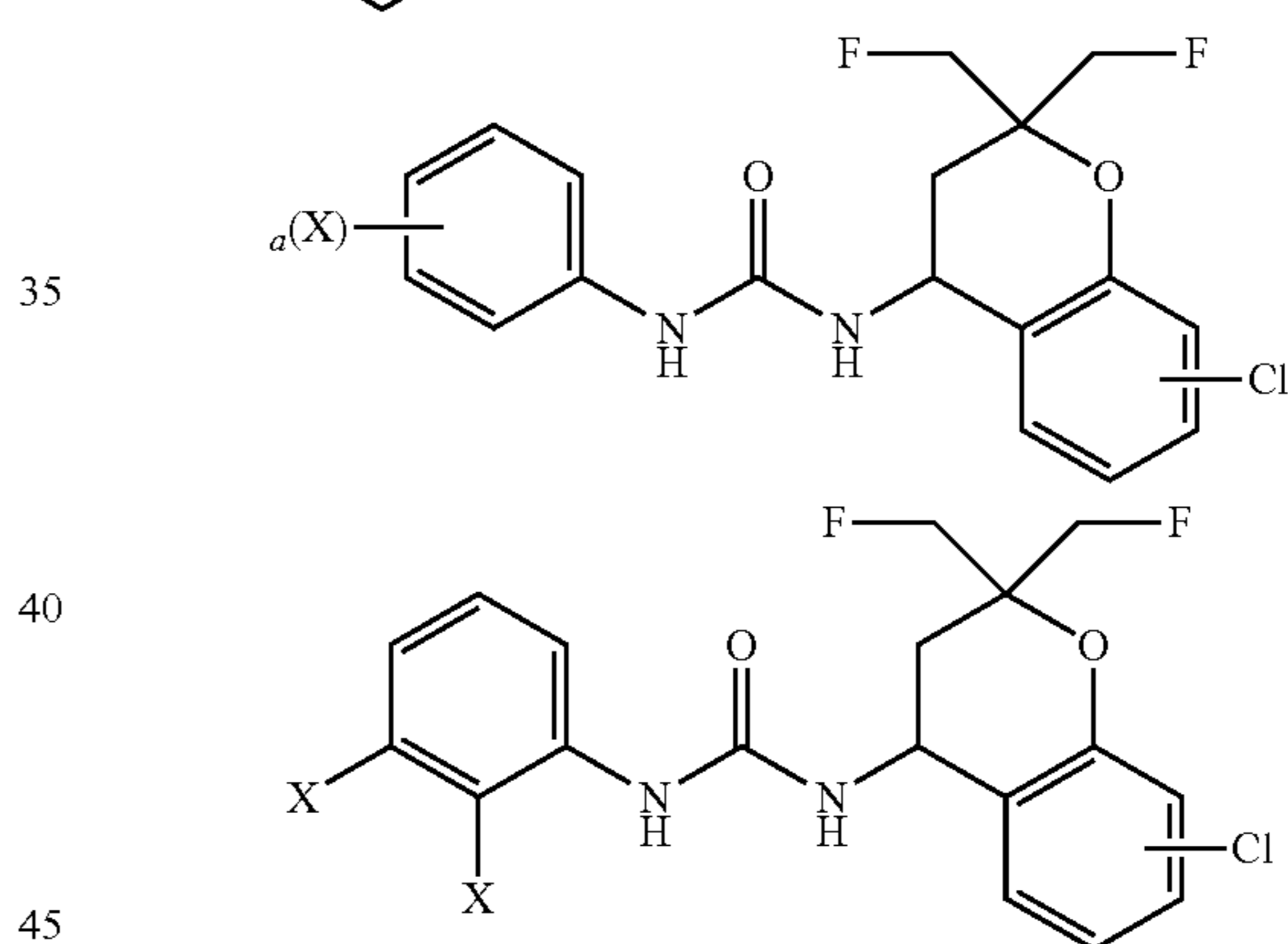
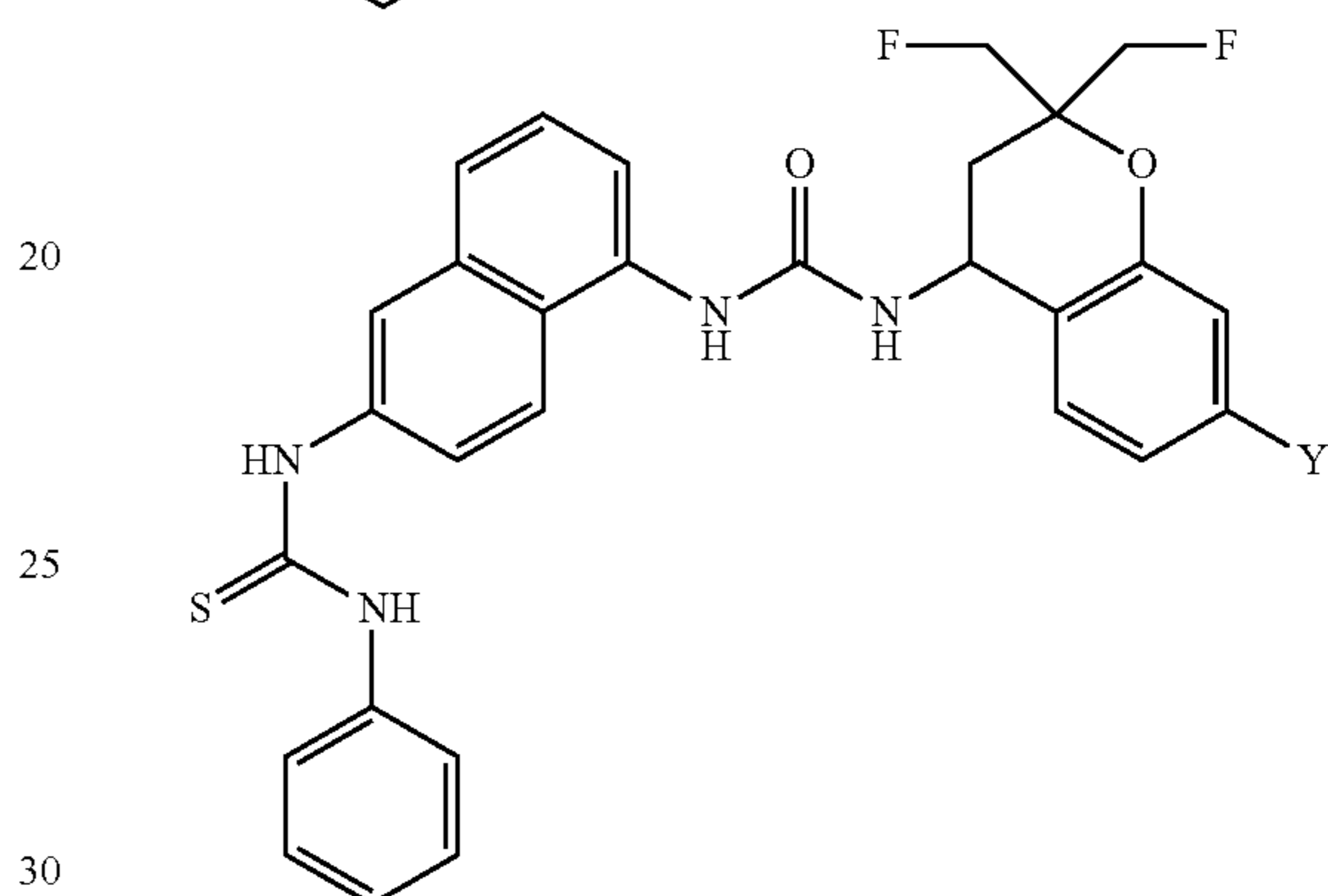
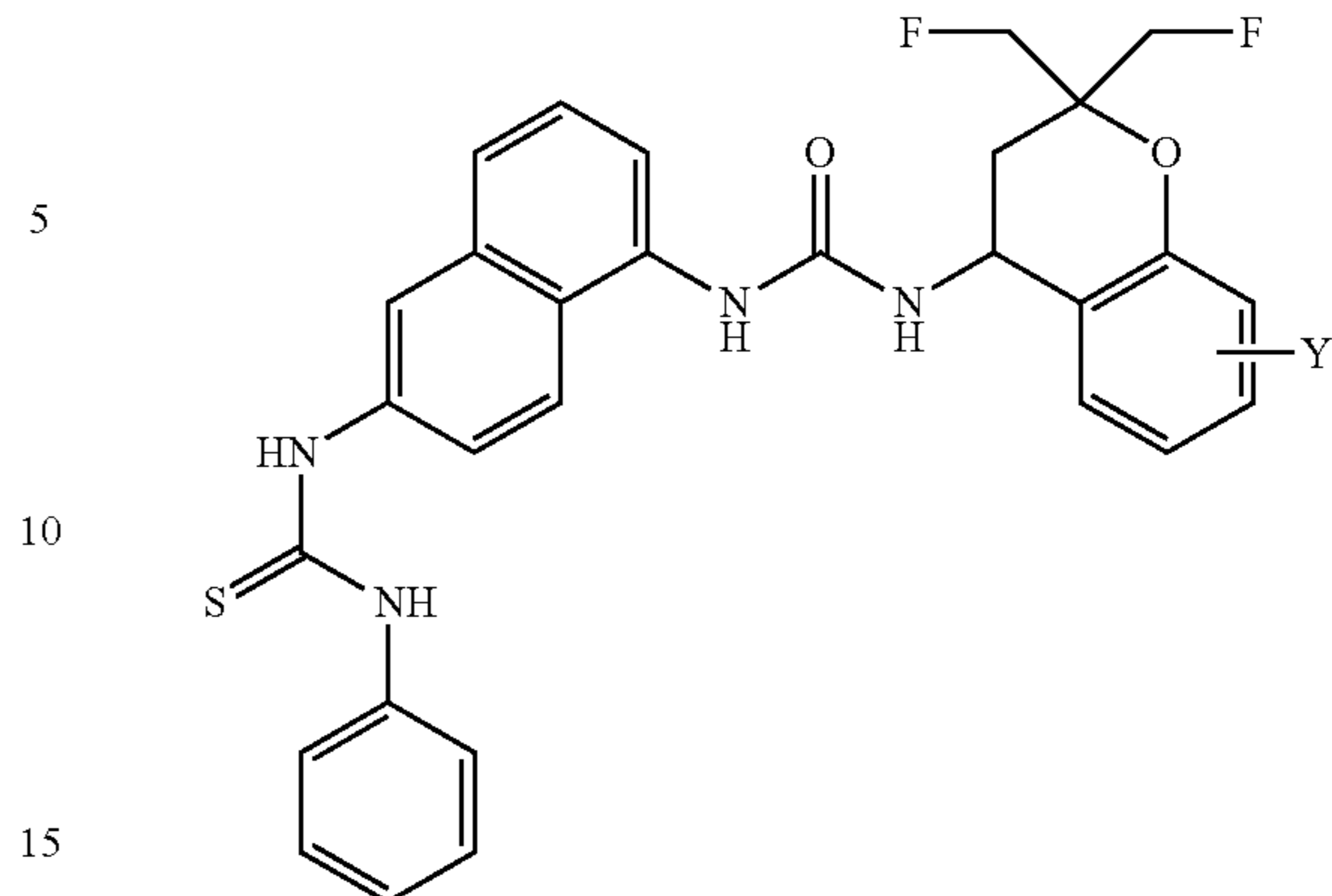


Compounds of Formulae (Ie) include:



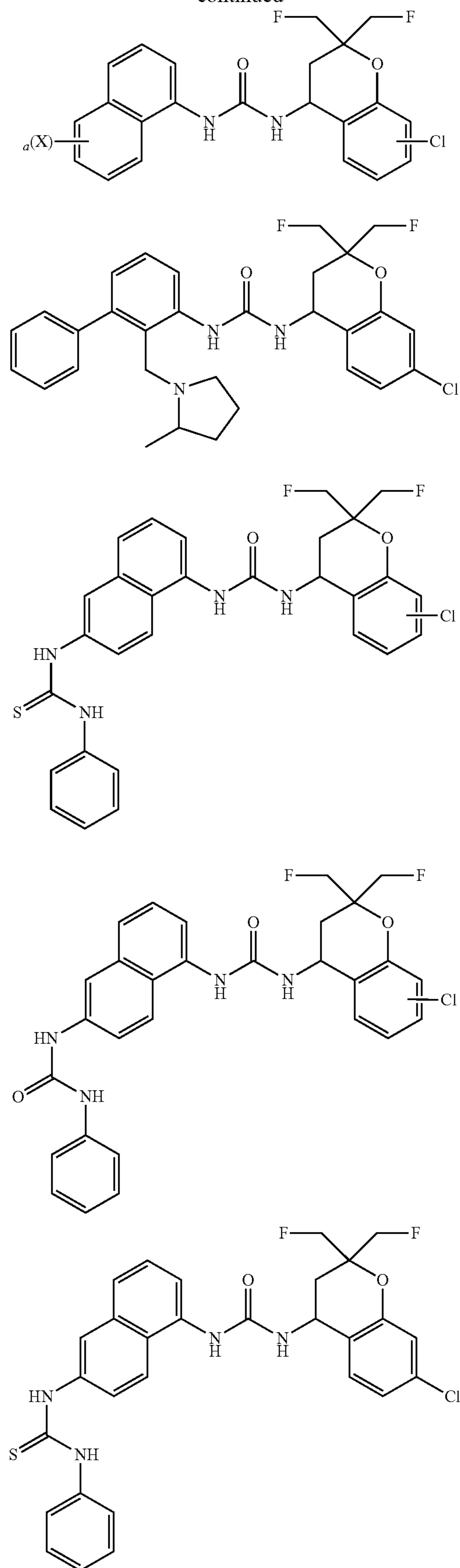
16

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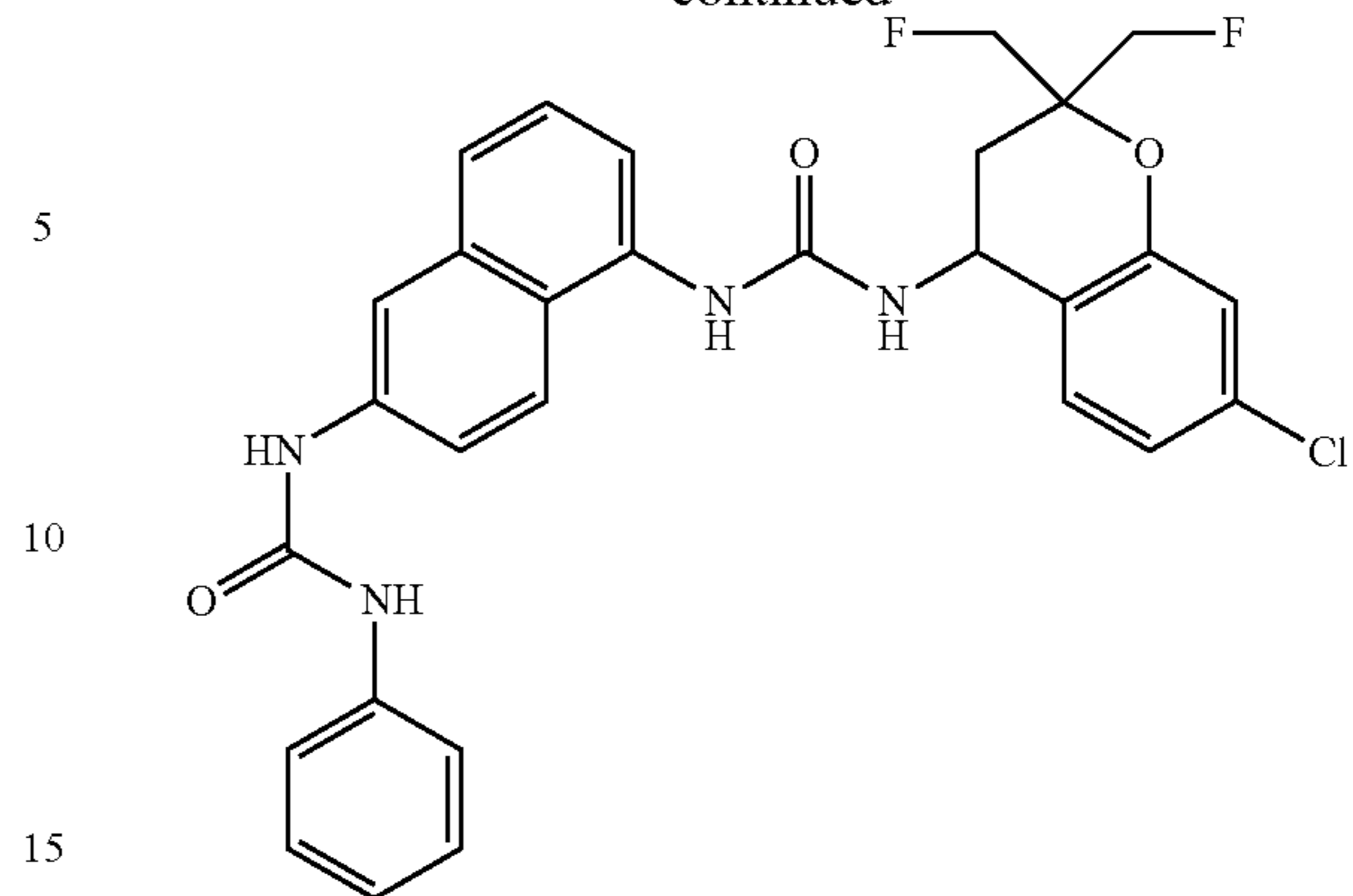
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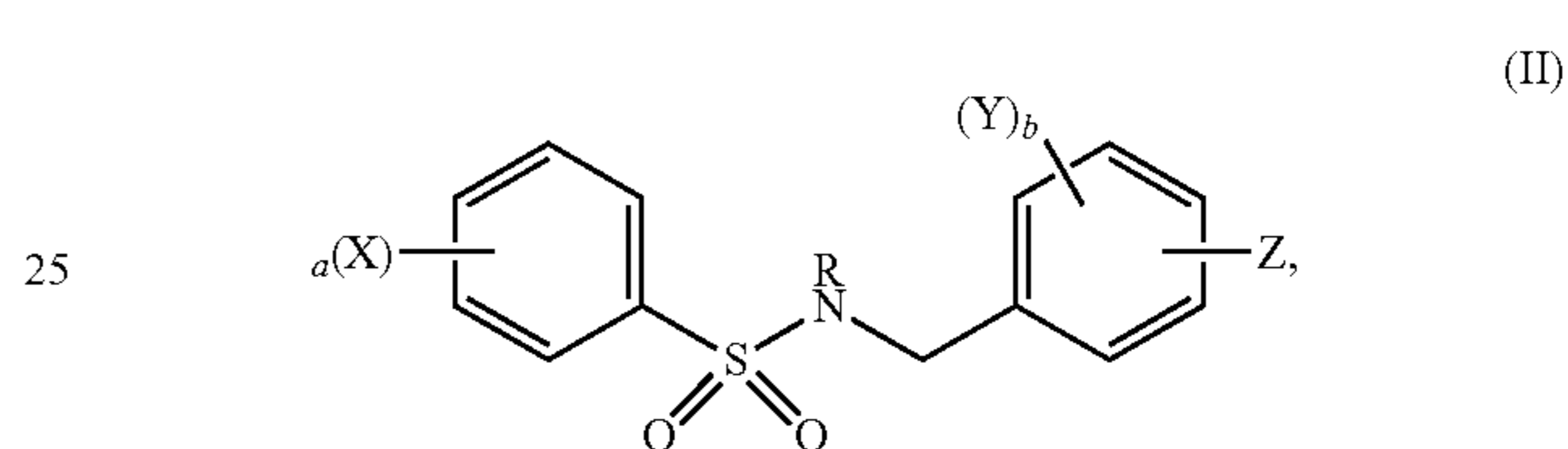
18

-continued



Compounds of the present disclosure also include novel compounds represented by Formula (II):

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wherein:

X is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₆)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Y is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₆)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Z is halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆)perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)

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haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R' is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆)perfluoroalkyl; (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

a is an integer of 0 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen,

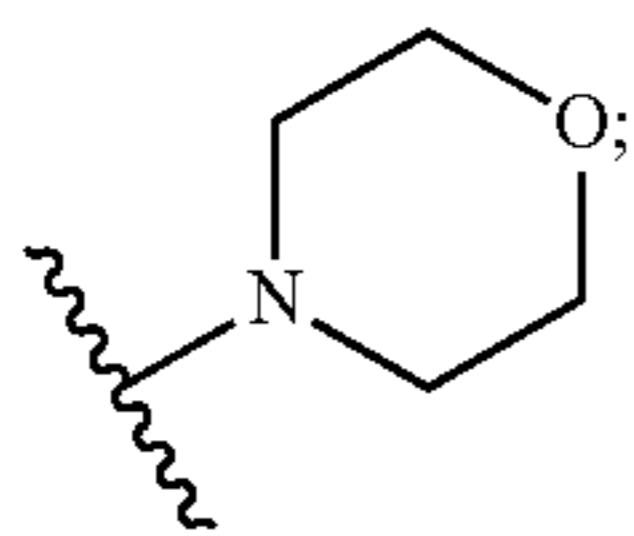
or a pharmaceutically acceptable salt or solvate thereof.

In some embodiments, in Formula (II),

X is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl;

Y is independently in each instance halogen, C₁-C₆ alkyl;

Z is N(R')₂, NO₂ or



R is independently in each instance H, C₁-C₆ alkyl;

R' is independently in each instance H, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl;

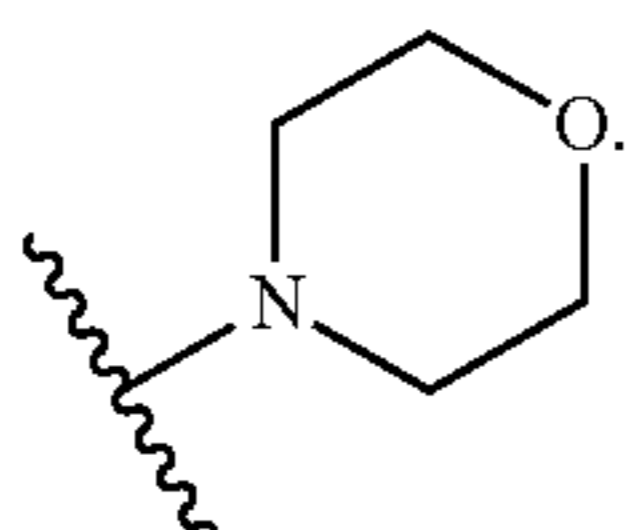
a is an integer of 1 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or any pharmaceutically acceptable salt or solvate thereof.

In some embodiments, the halogen is fluoro.

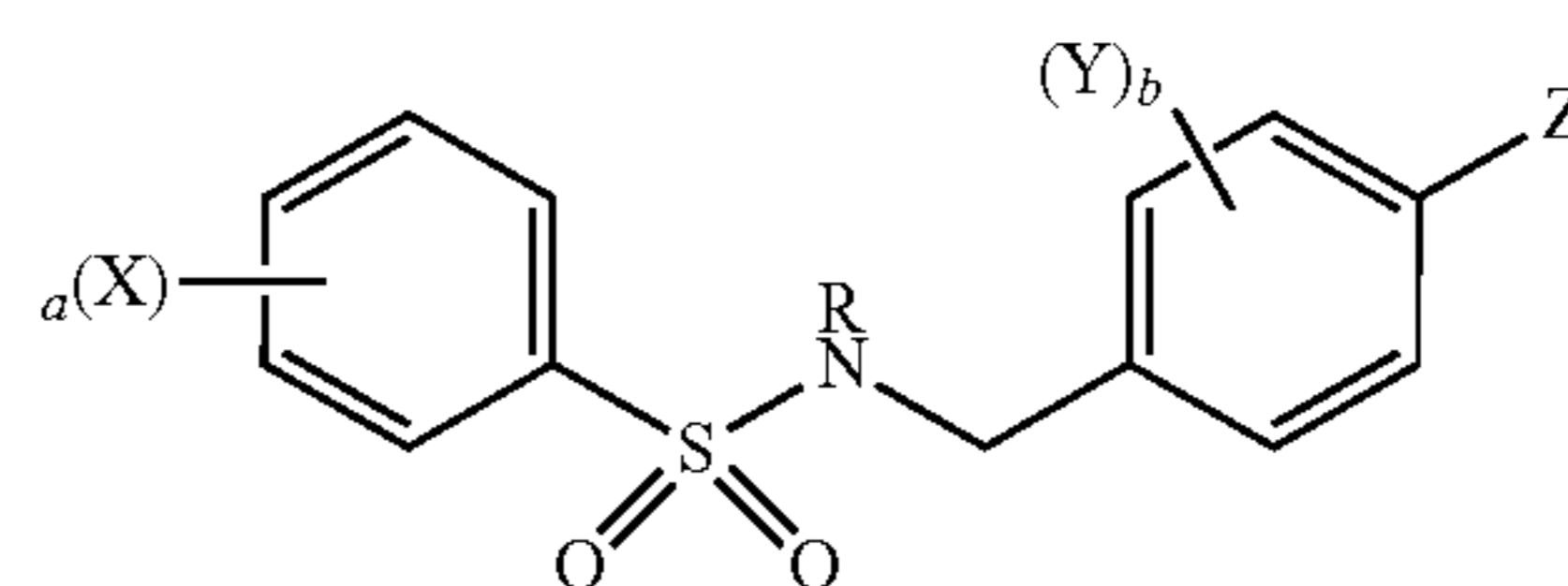
In some embodiments, Z is N(R')₂ or NO₂ or



In some embodiments, a is an integer of 1 to 5; and b is an integer of 0 to 4.

In some embodiments, the compounds of the present disclosure include novel compounds represented by Formula (IIa):

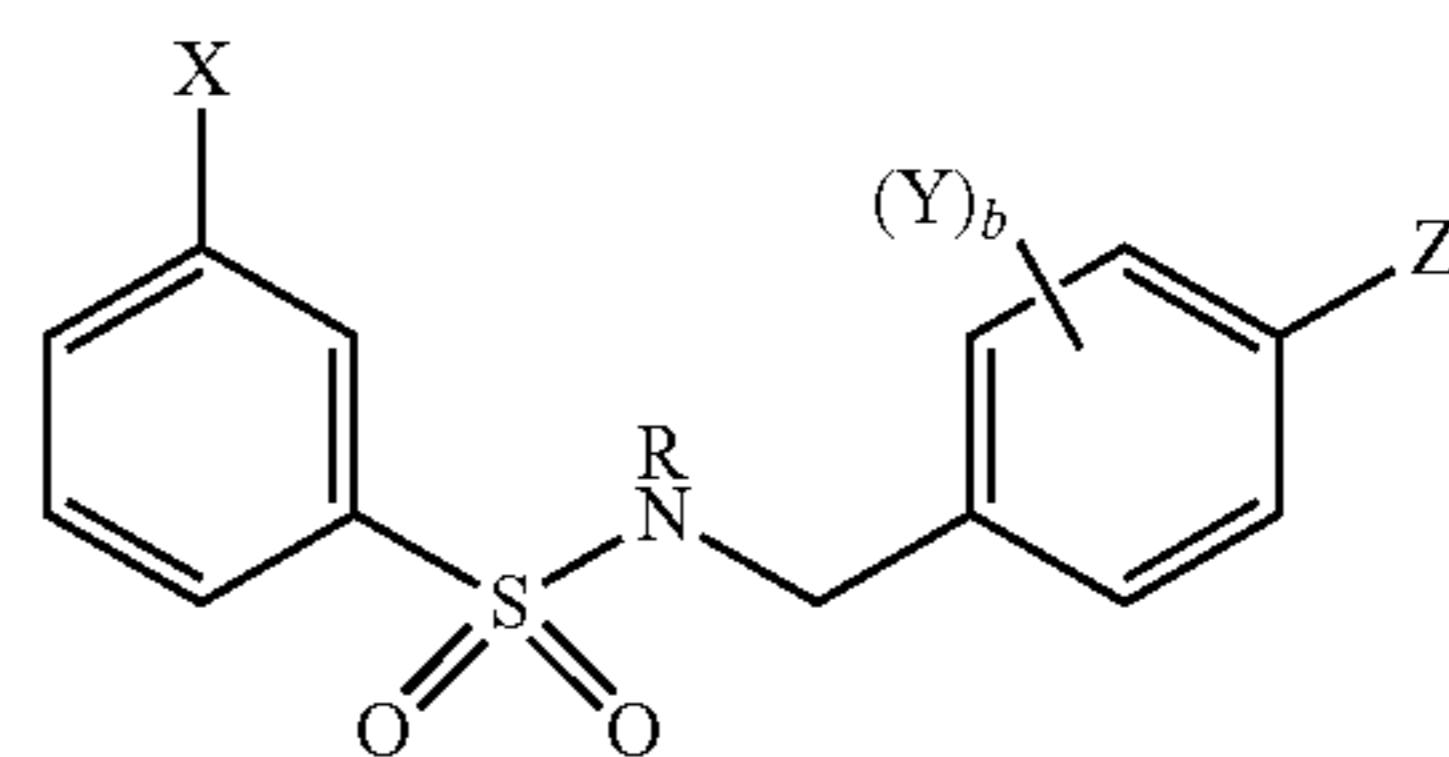
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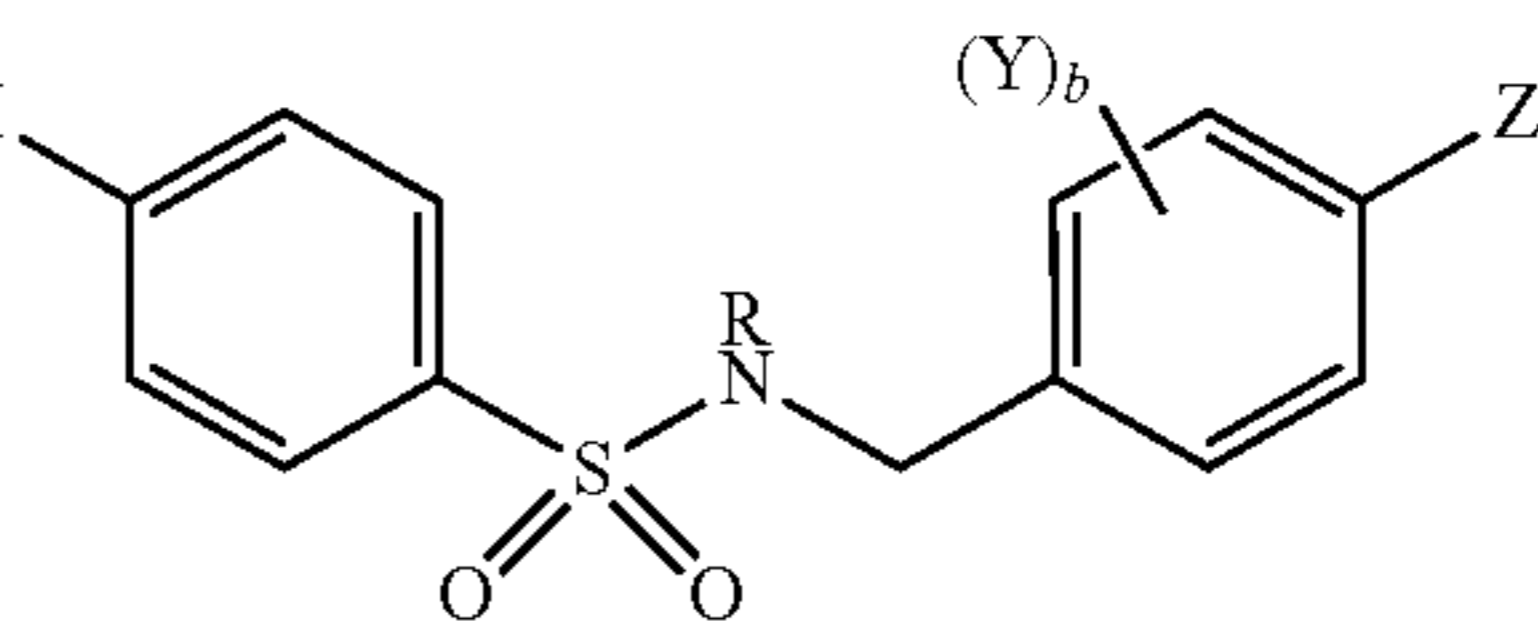
(IIa)

or any pharmaceutically acceptable salt or solvate thereof.

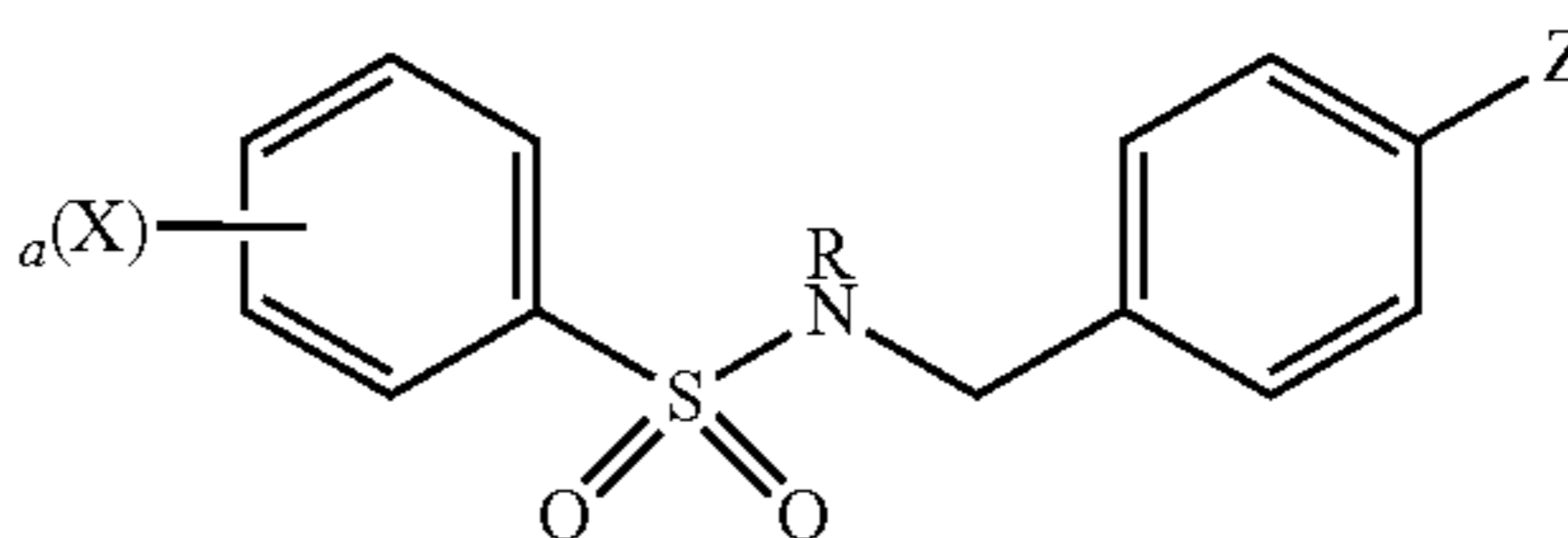
In further embodiments, the compounds of the present disclosure include novel compounds represented by Formula (IIa') or (IIa'') or (IIa''') or (IIa''') or (IIa'''):



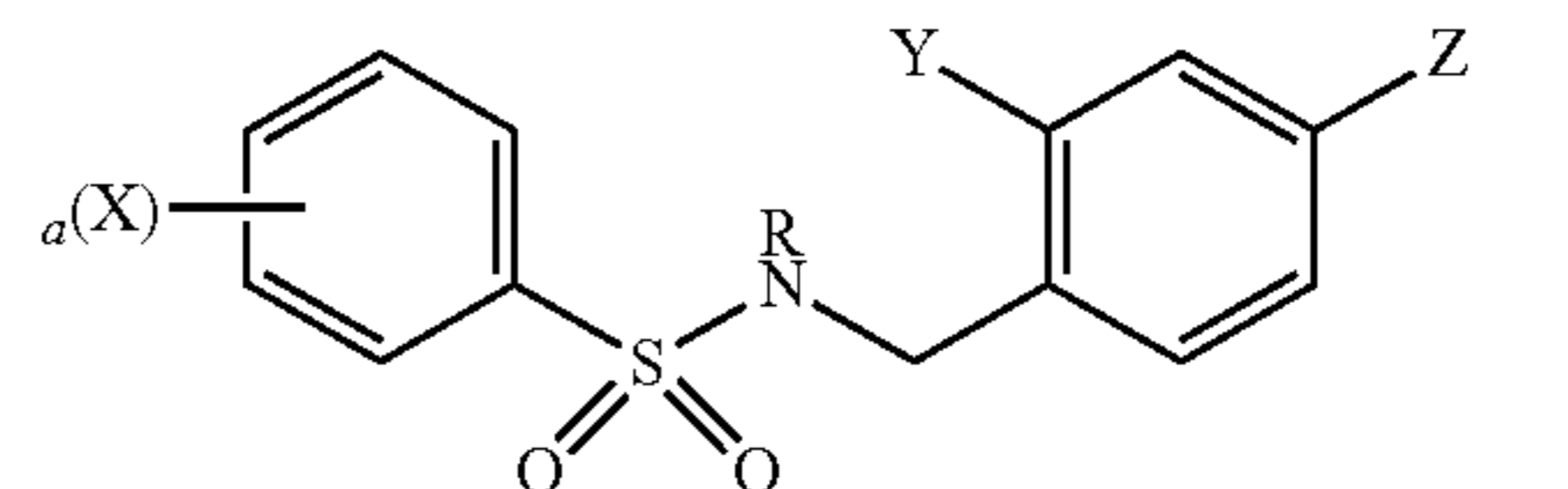
(IIa')



(IIa'')

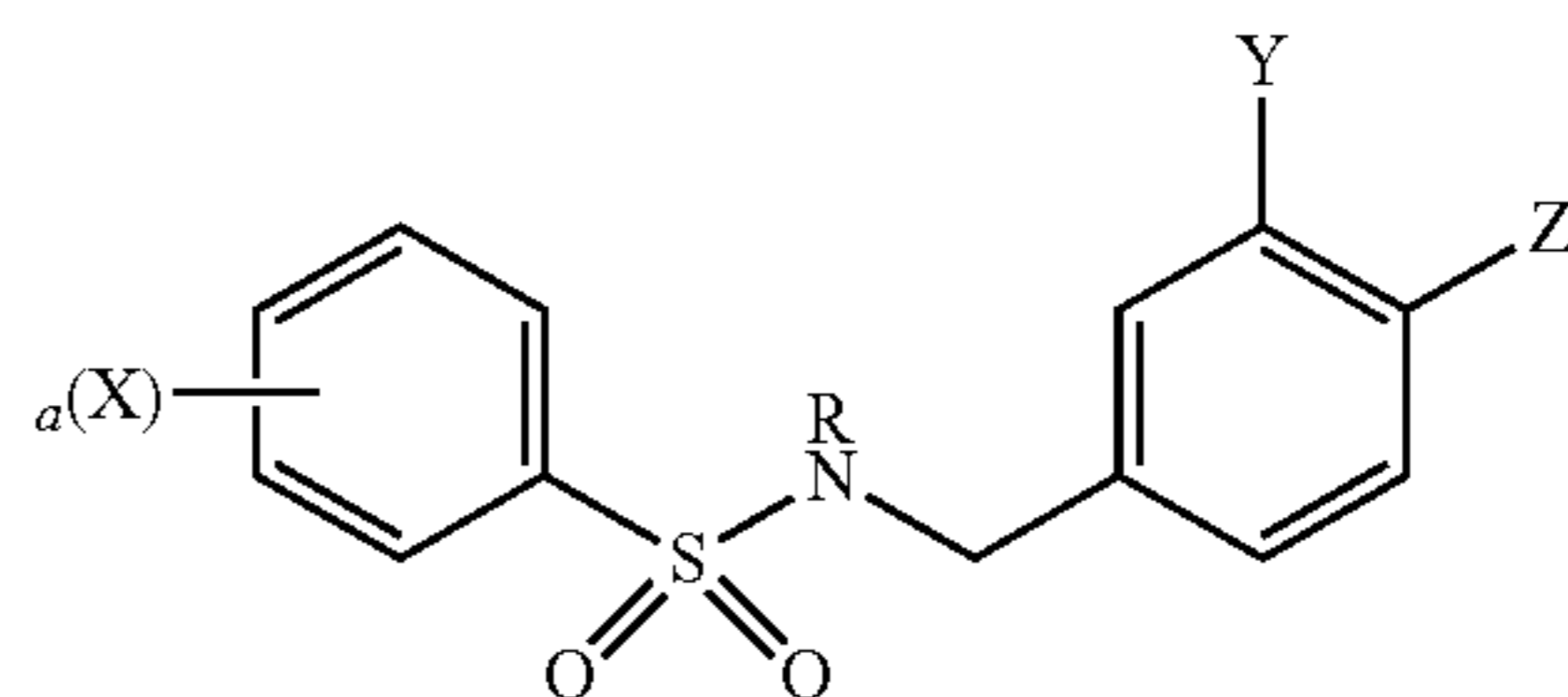


(IIa''')



(IIa''')

and



(IIa''')

or any pharmaceutically acceptable salt or solvate thereof.

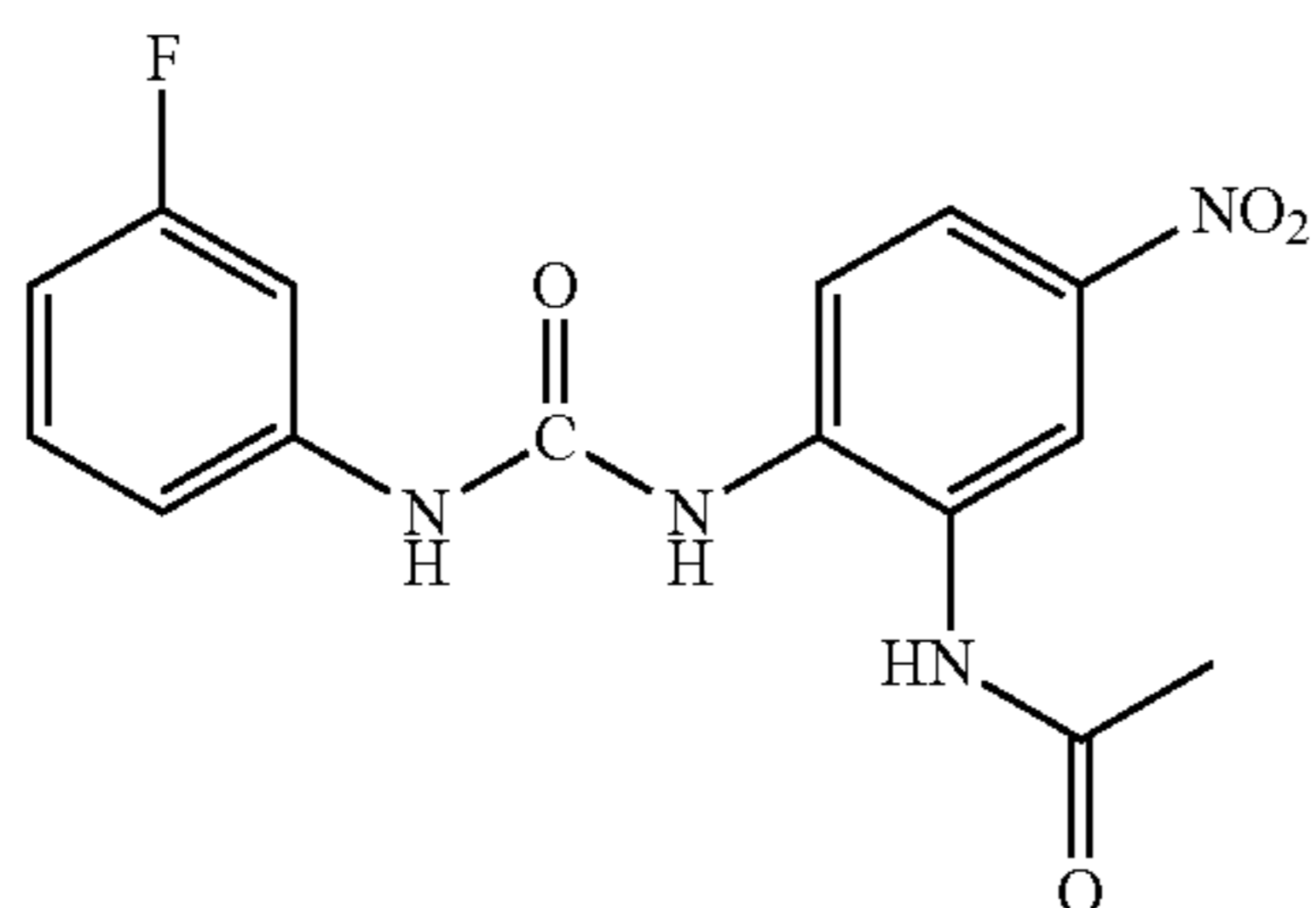
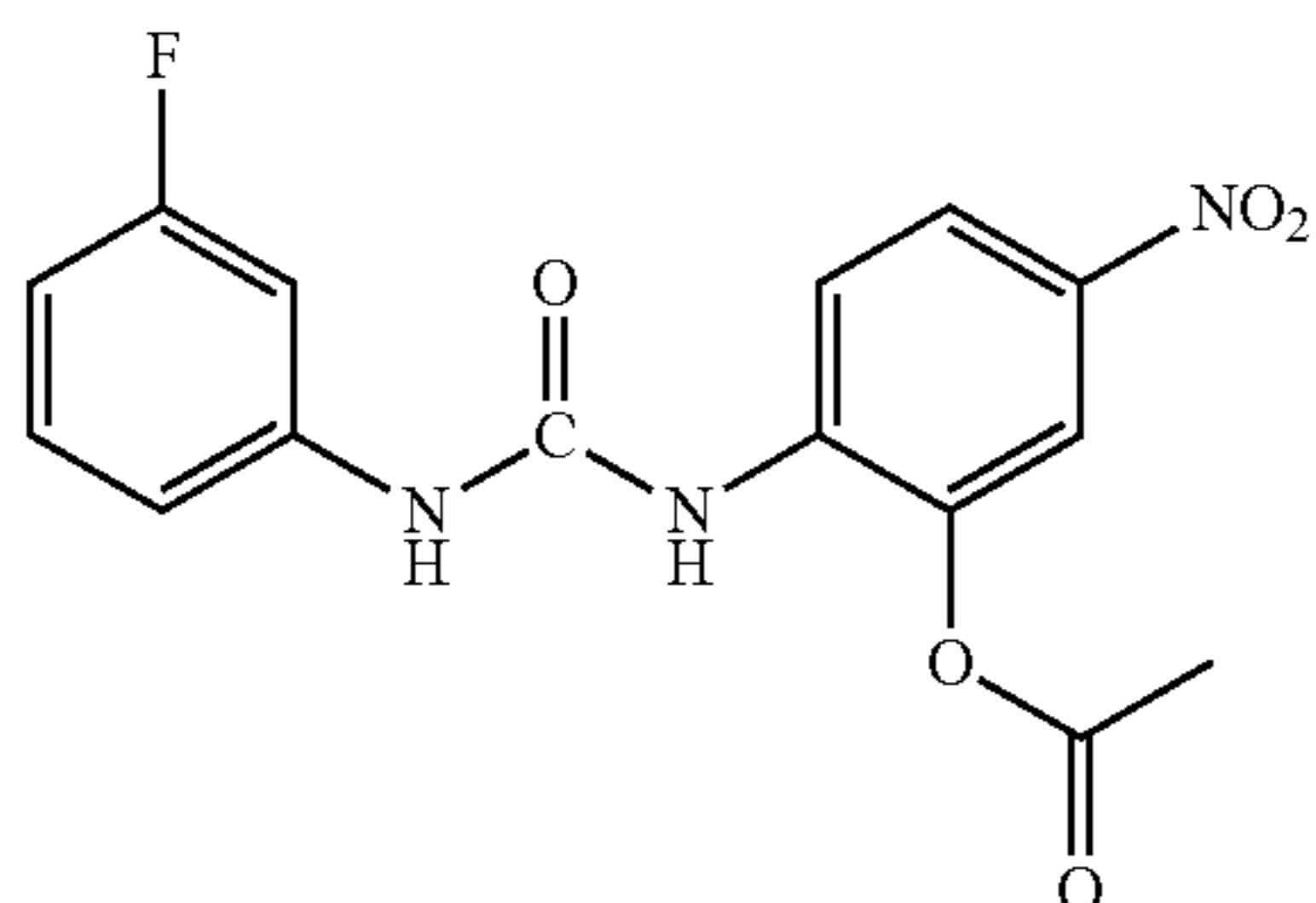
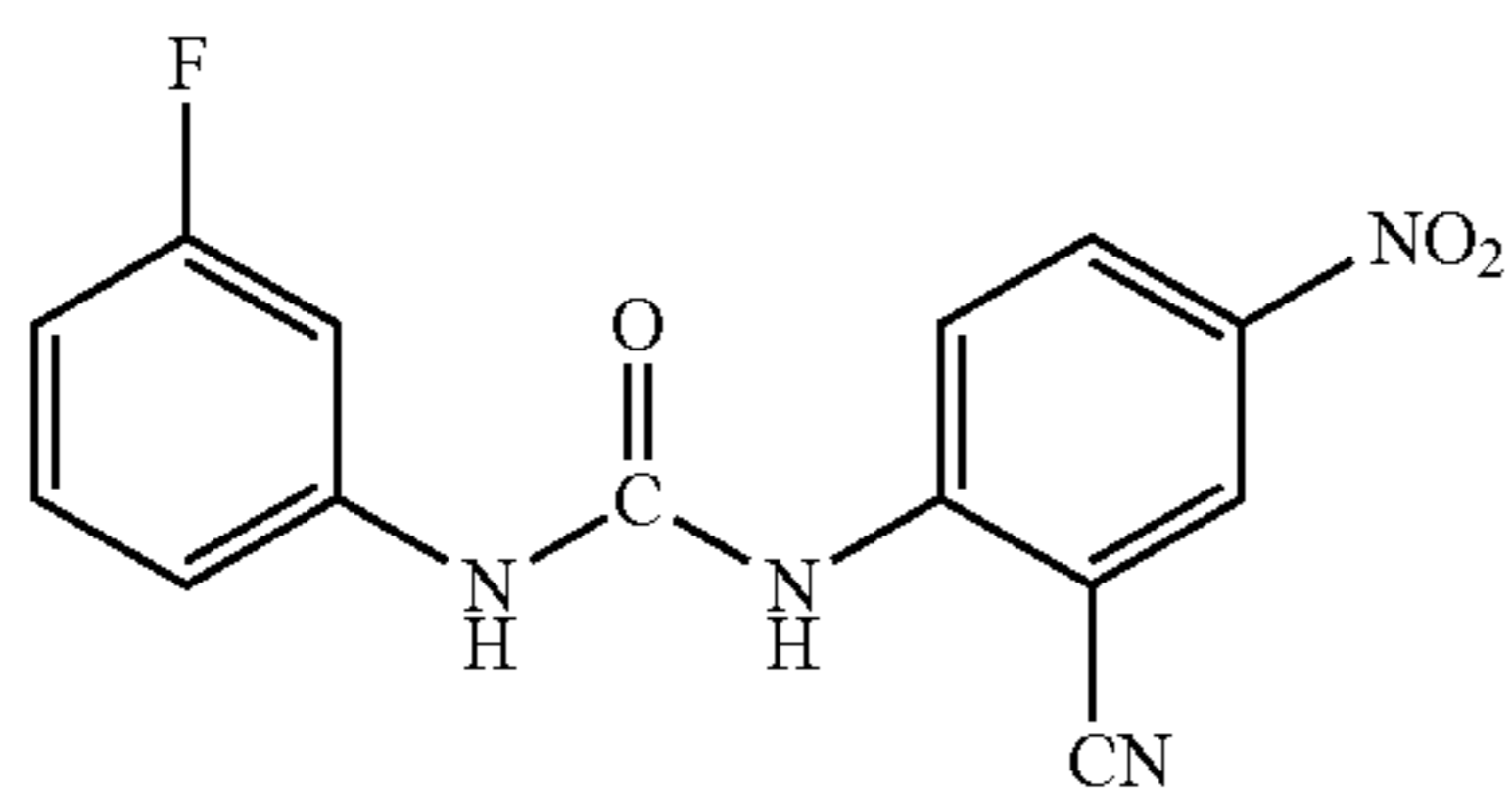
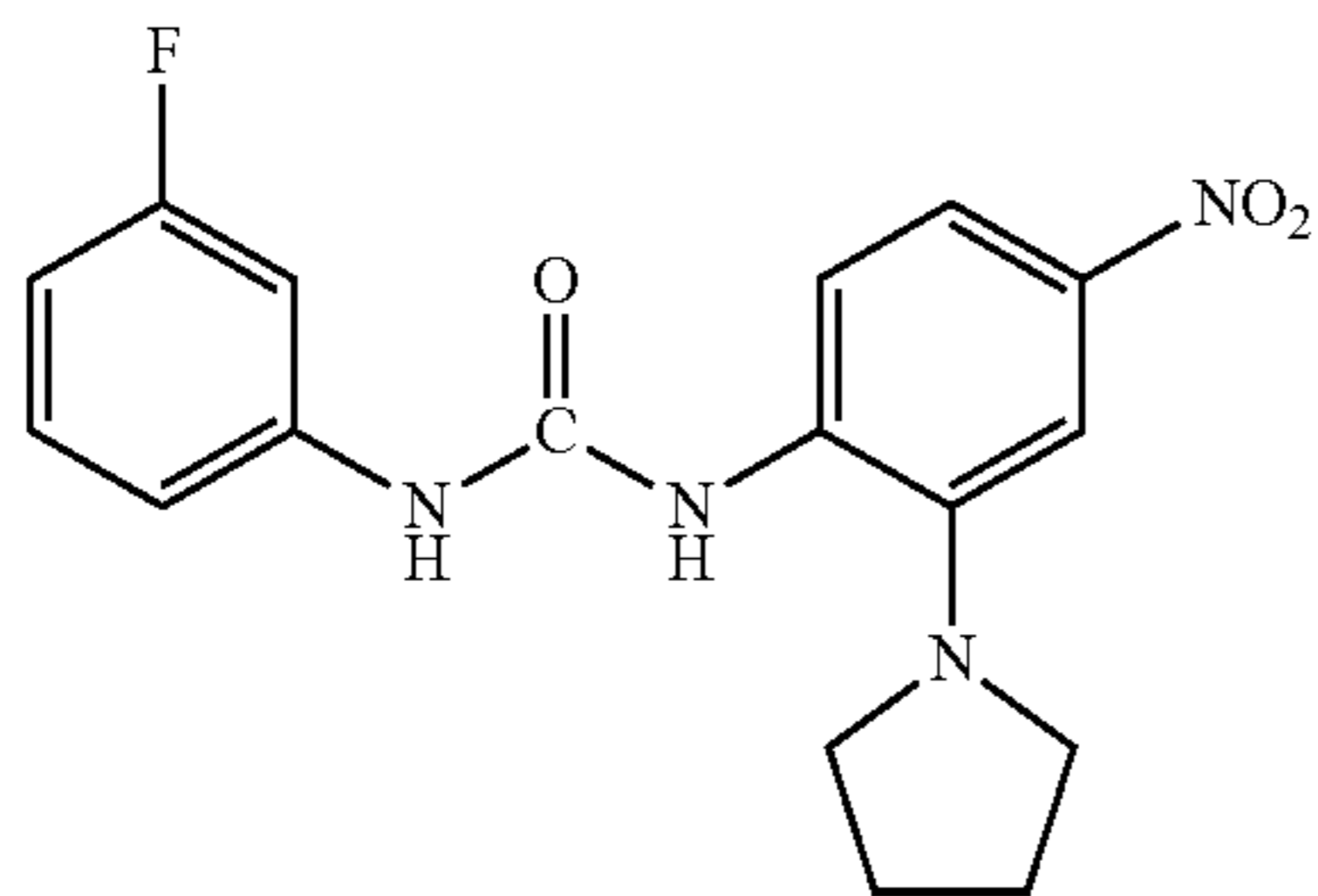
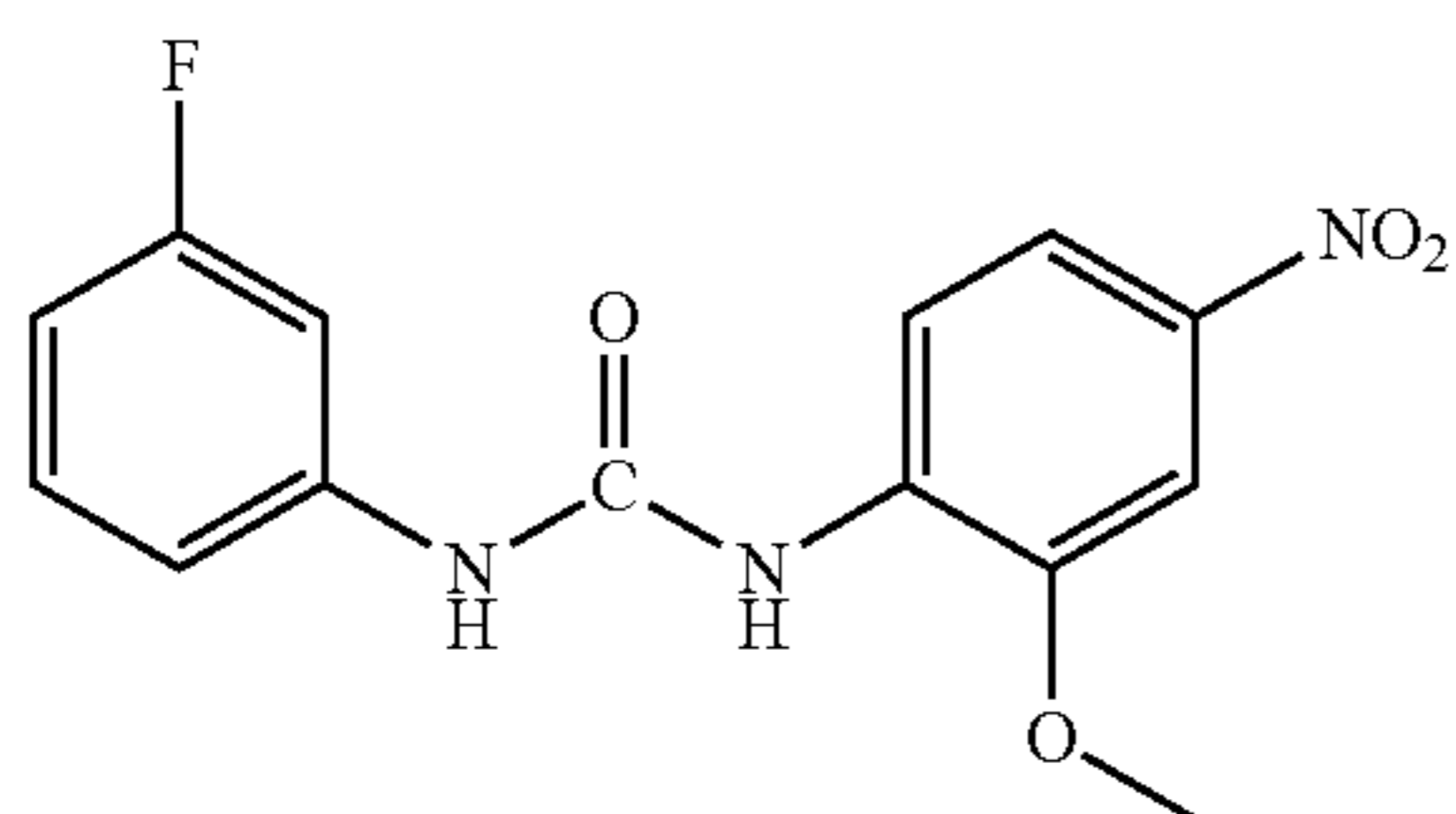
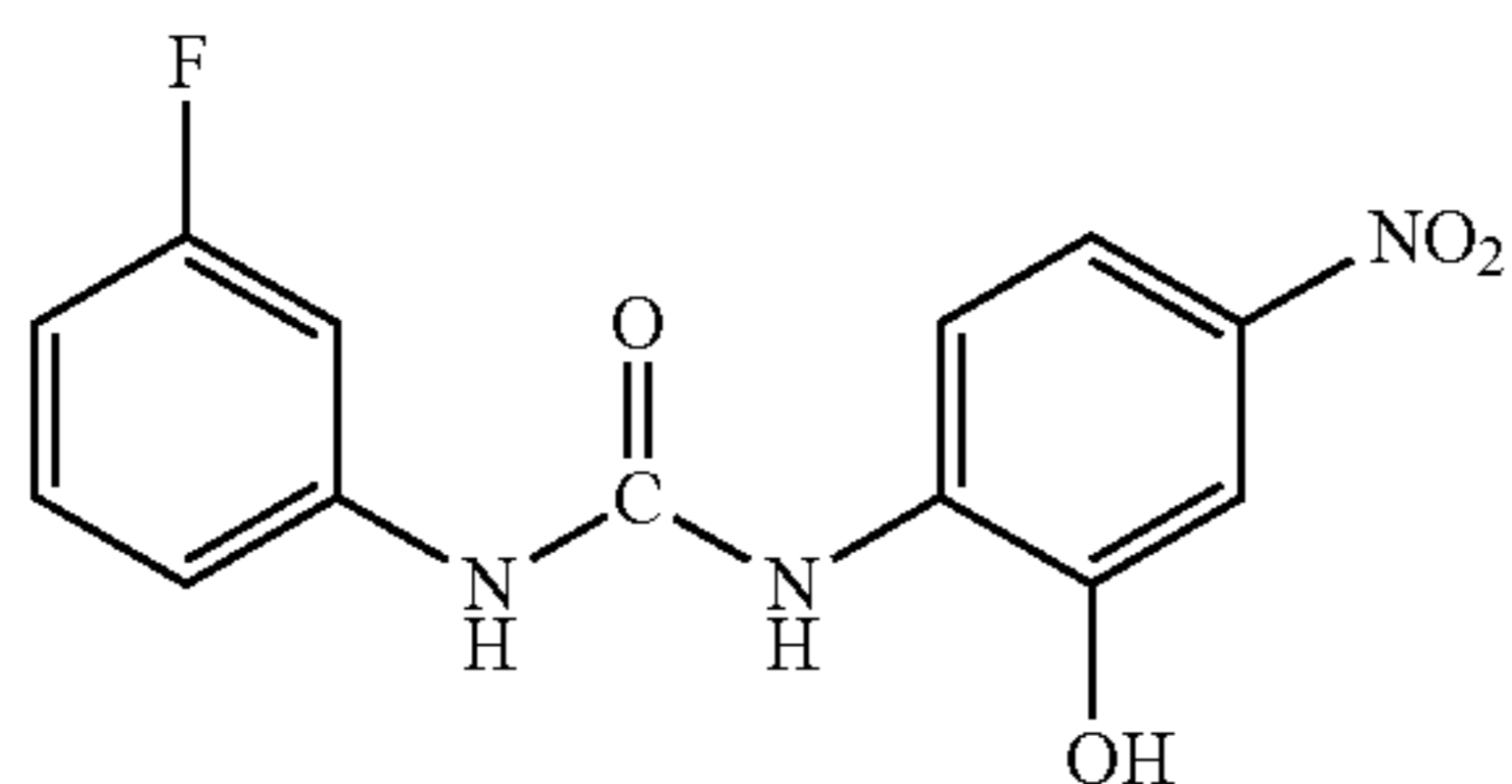
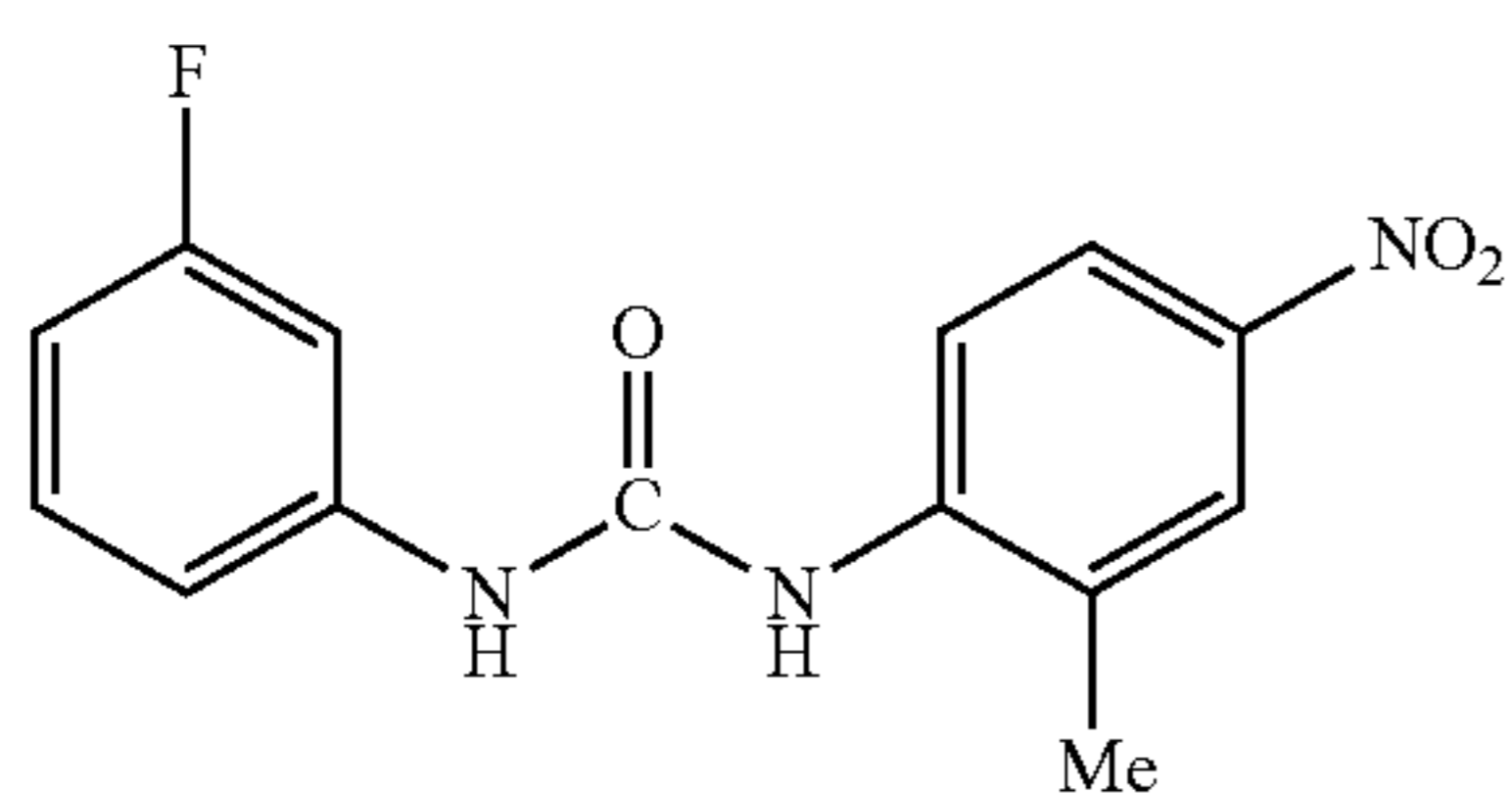
The variables of formulae (IIa), (IIa'), (IIa''), (IIa'''), (IIa'''), and (IIa''') are the same as for Formula (II).

In some embodiments of the Formulae (I) and (II) and their sub-formulae, the C₁-C₆ alkyl is one or more of methyl, ethyl, propyl (n-, i-), butyl (n-, i-, t-, sec-), pentyl or hexyl. Preferred embodiments include methyl and ethyl. When the C₁-C₆ alkyl is substituted by one or more halogen, the embodiments include, for example, —CH₂F, —CHF₂, —CF₃, —CH₂CH₂F, —CH₂CHF₂, —CH₂CF₃, —CHFCH₃, —CHFCH₂F, —CHFCHF₂, —CHFCH₂F, —CF₂CH₃, —CF₂CH₂F, —CF₂CHF₂, —CF₂CF₃.

In some embodiments, the C₁-C₆ perfluoroalkyl is a —CF₃ or —CF₂CF₃. In some embodiments, a is 0 or 1 or 2 or 3 or 4 or 5. In a preferred embodiment, a is 1. In some embodiments, b is 0 or 1 or 2 or 3 or 4. In a preferred embodiment, b is 0 or 1.

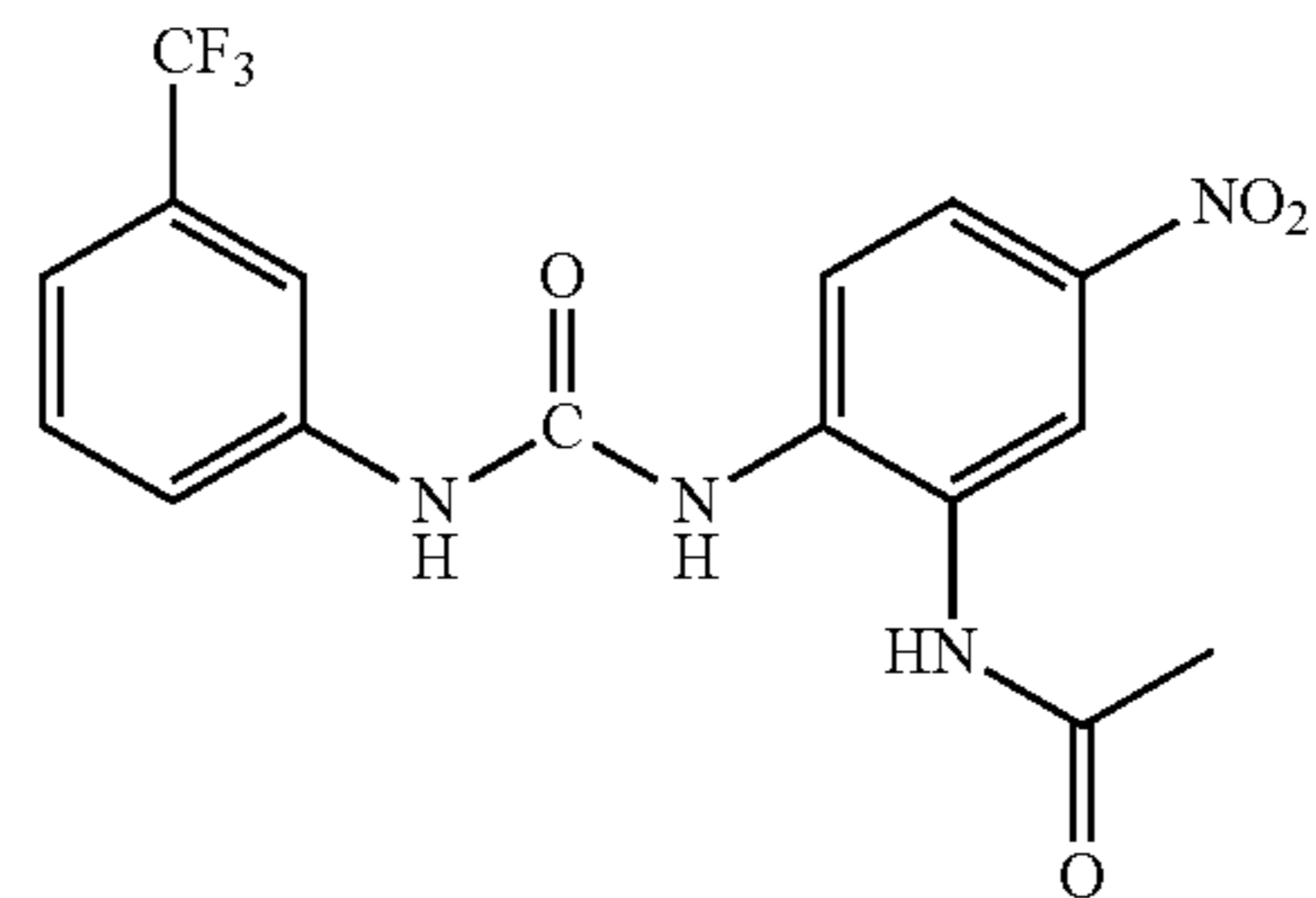
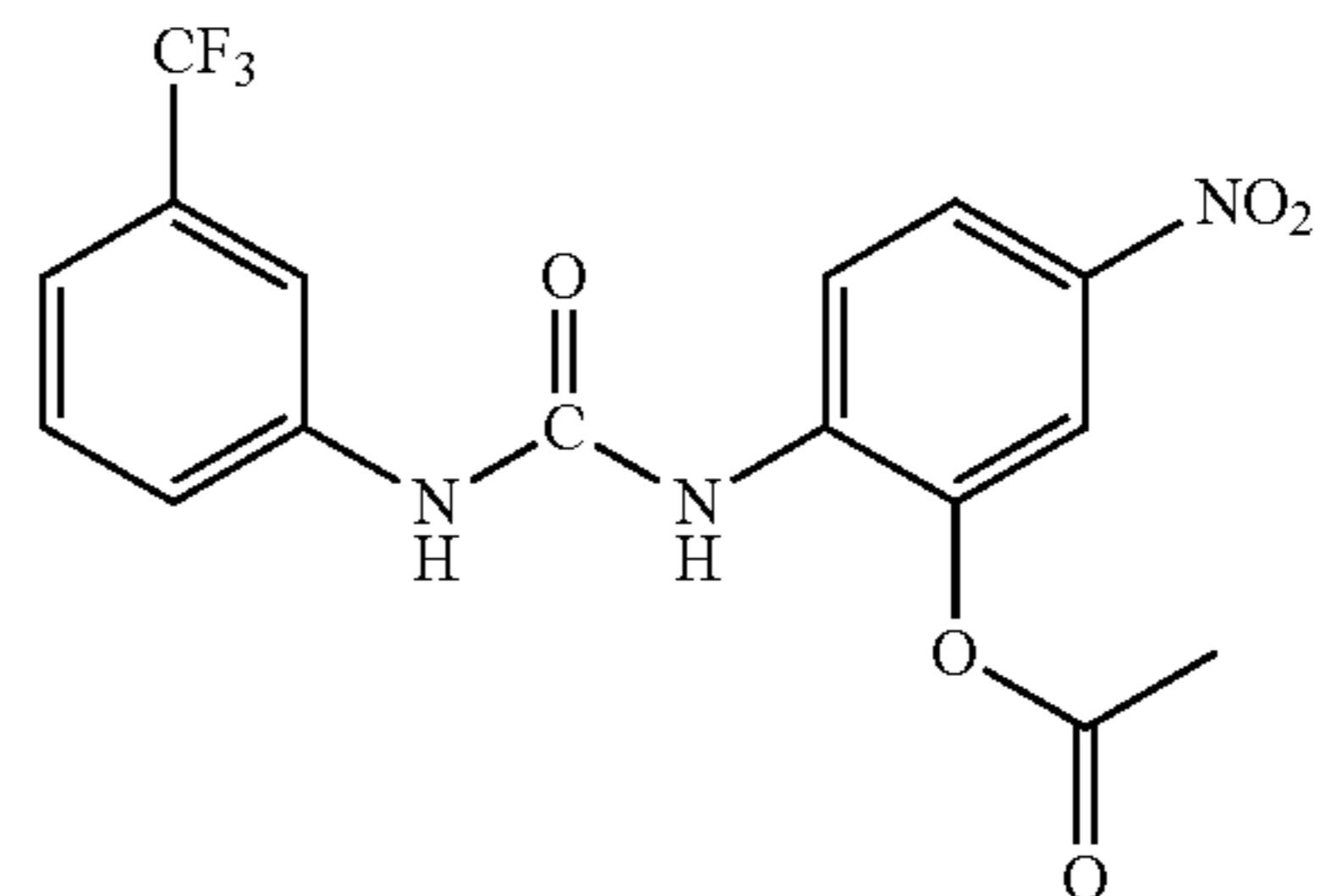
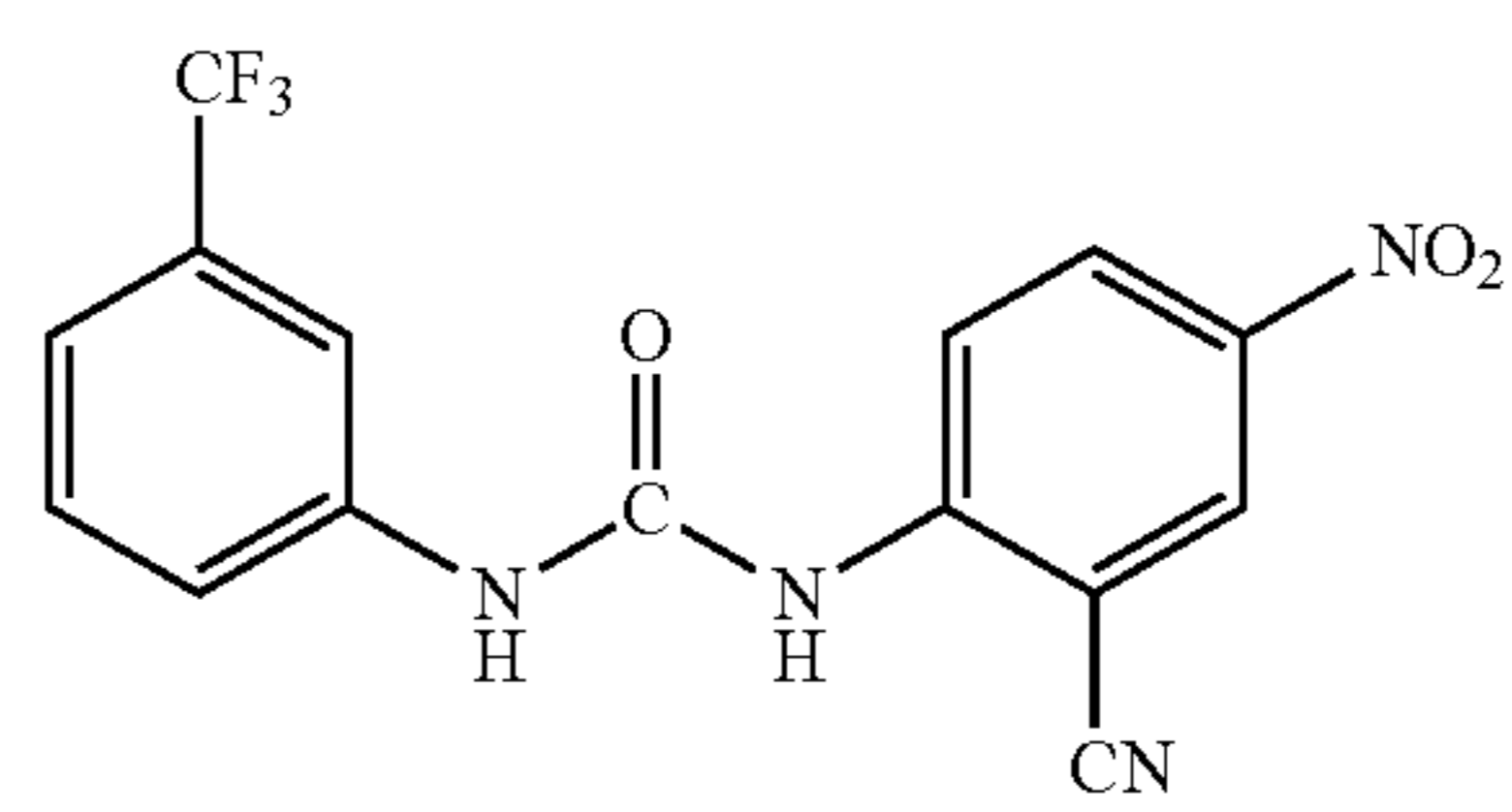
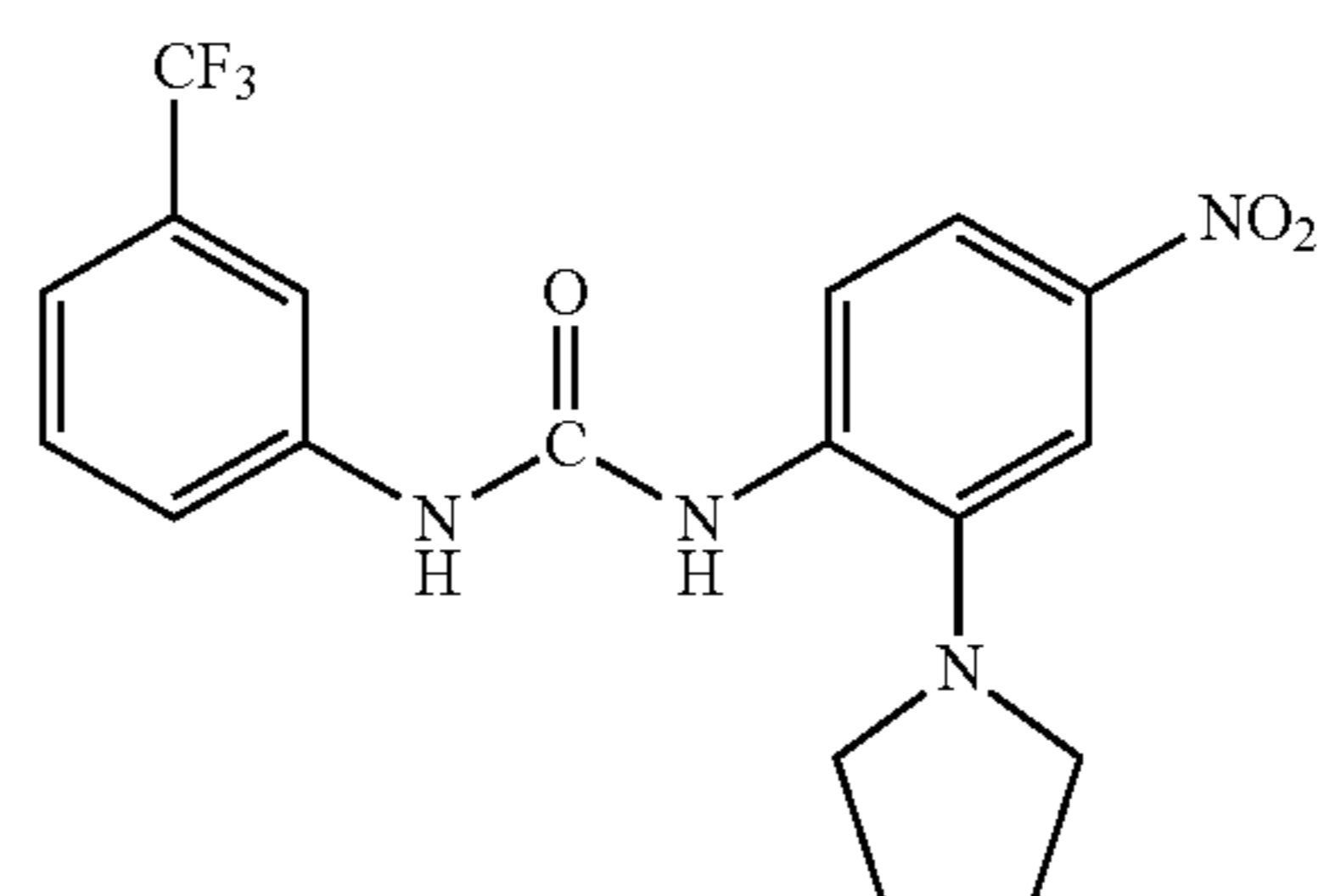
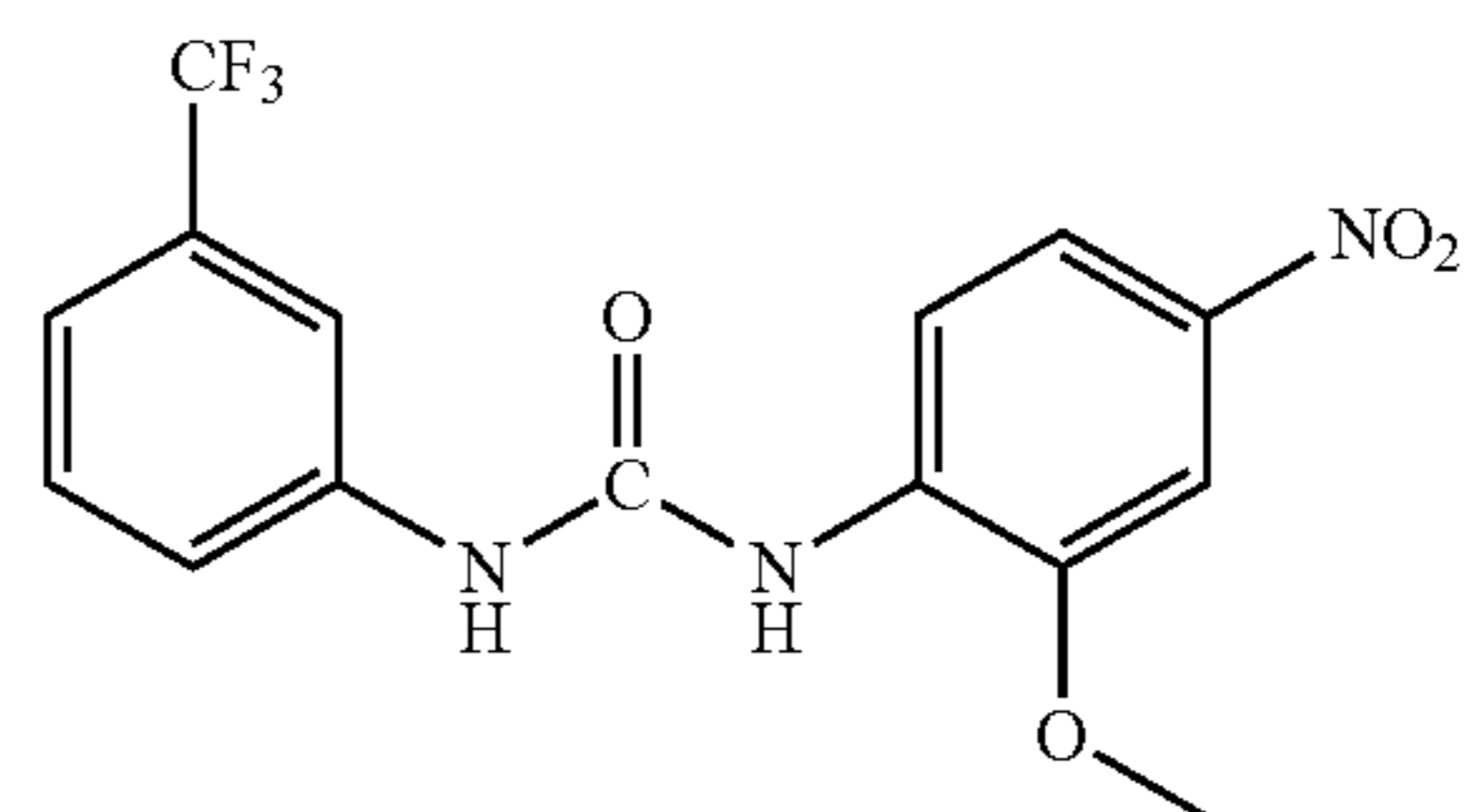
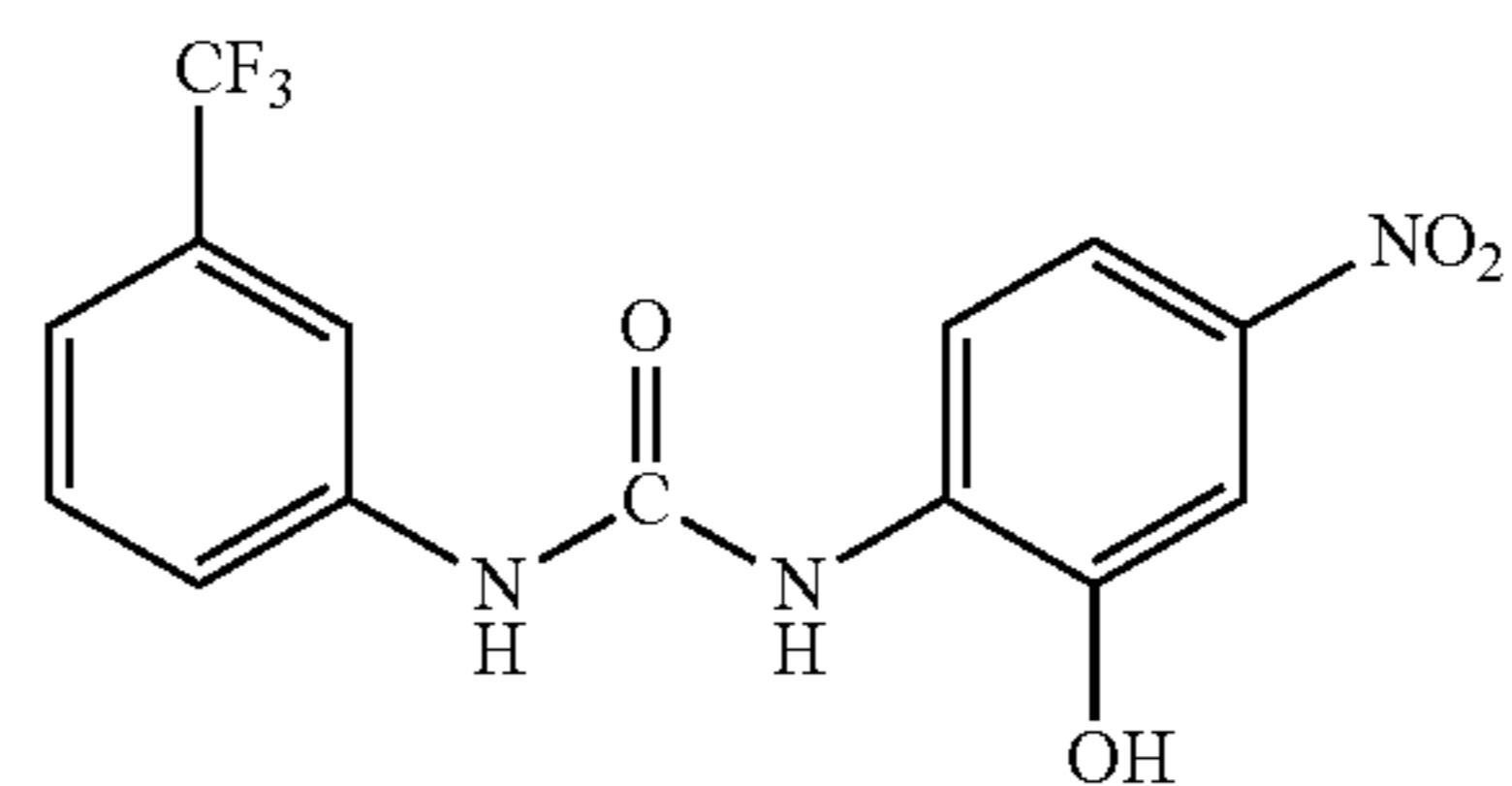
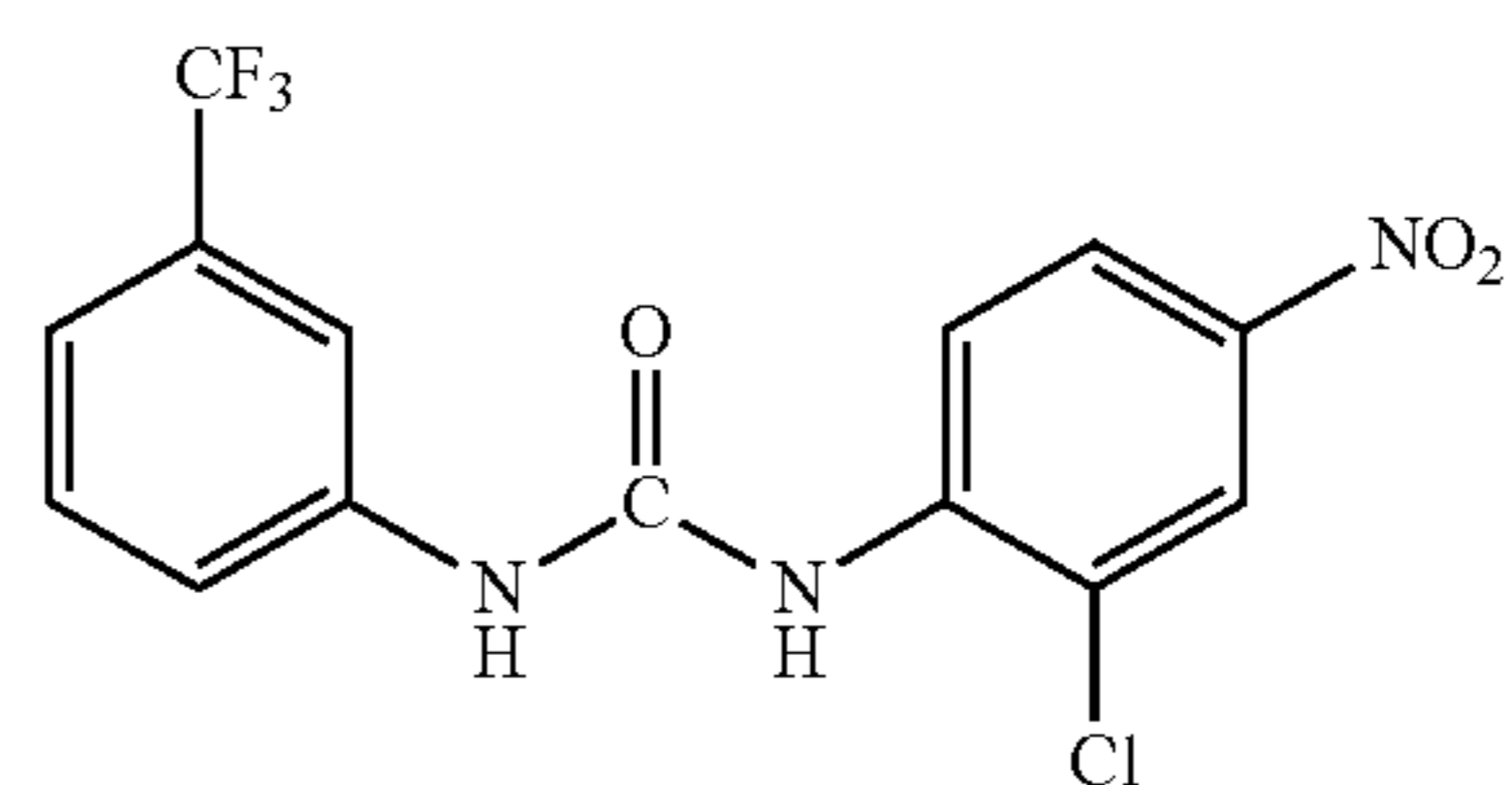
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Specific embodiments of compounds of the present invention include:



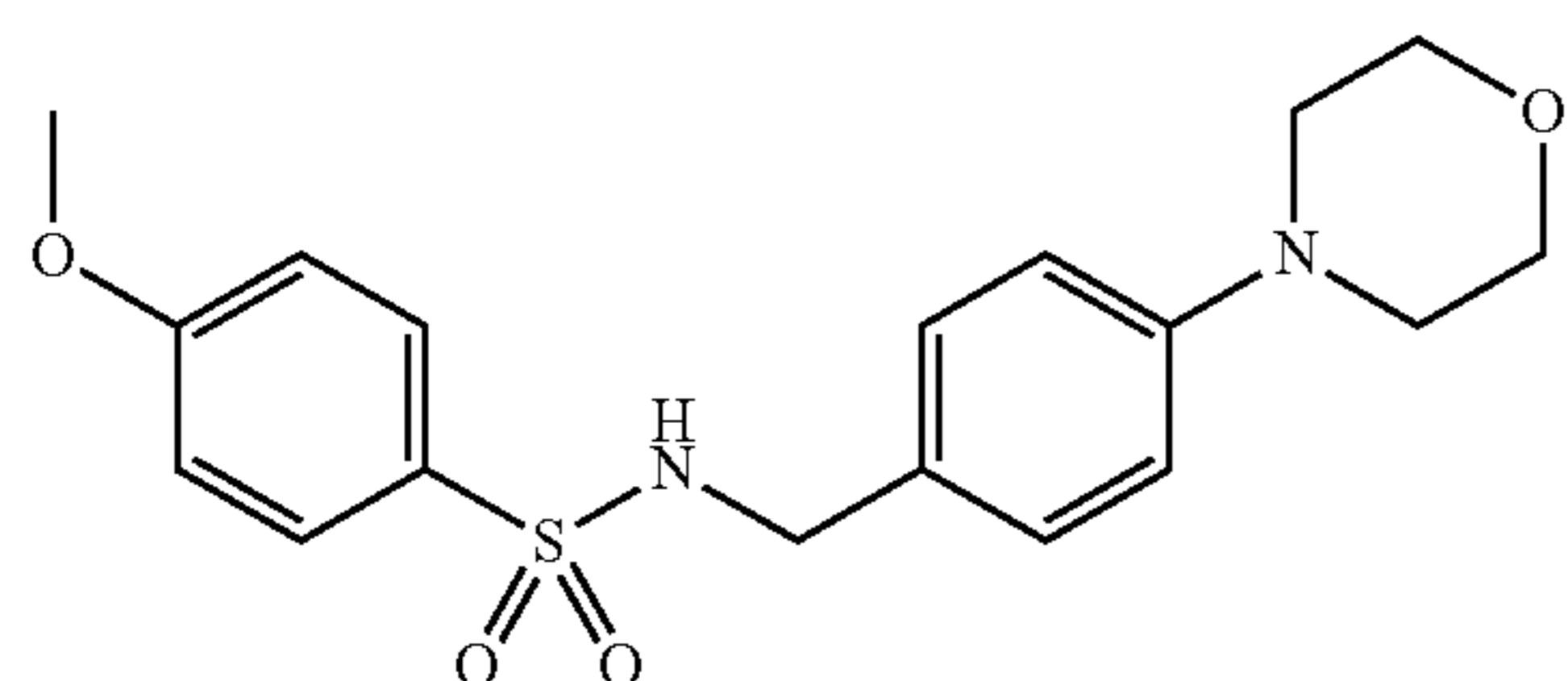
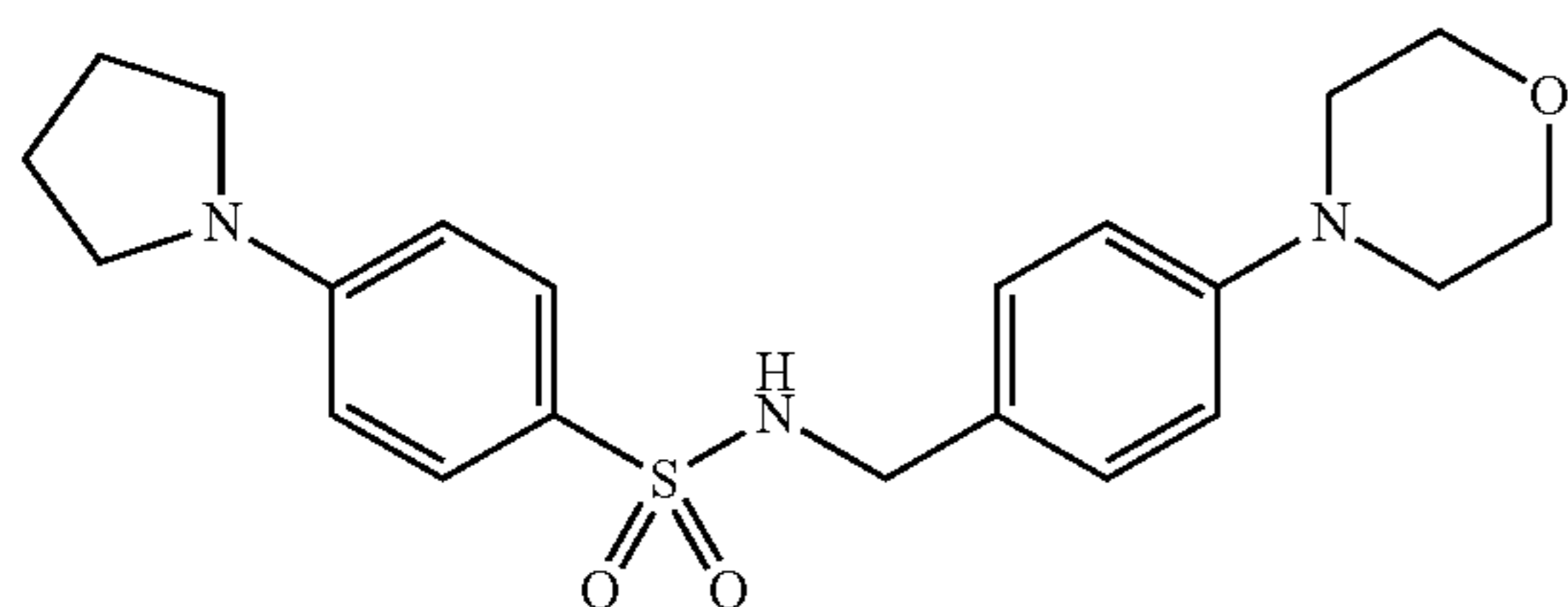
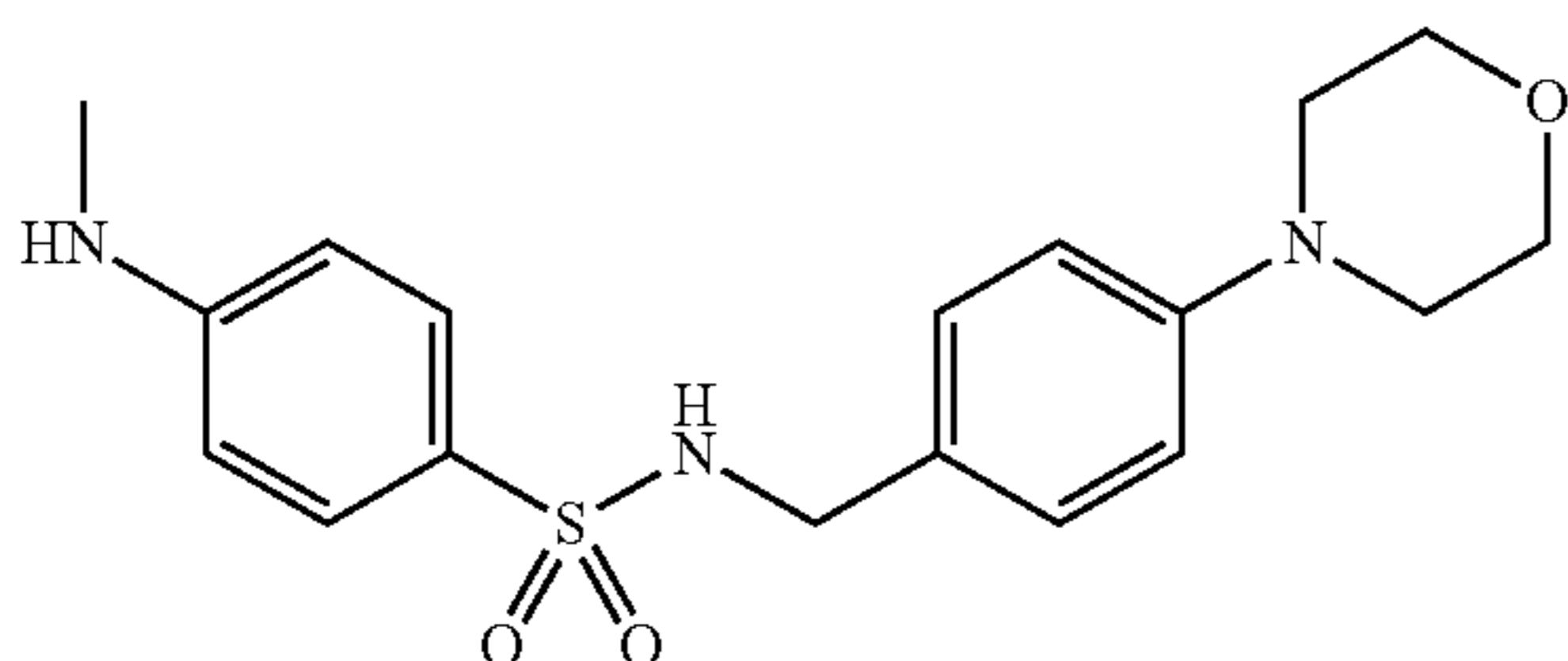
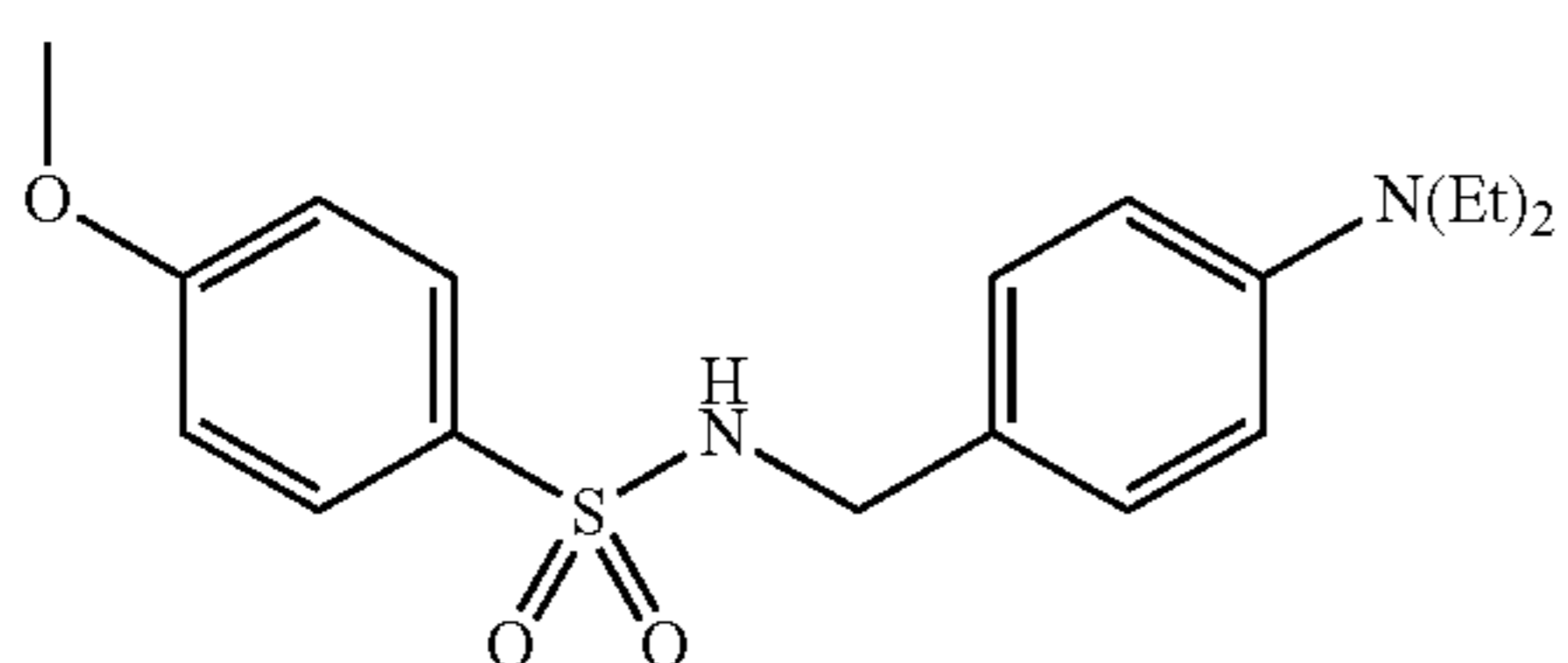
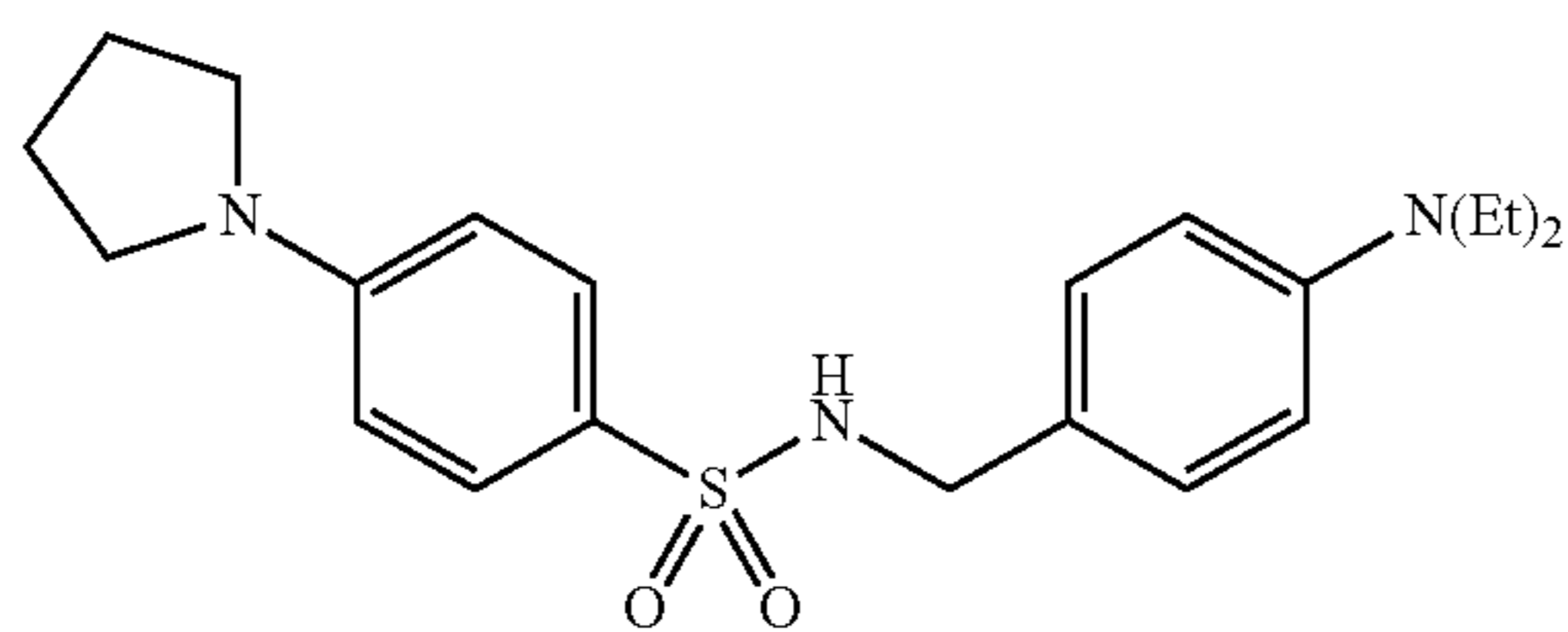
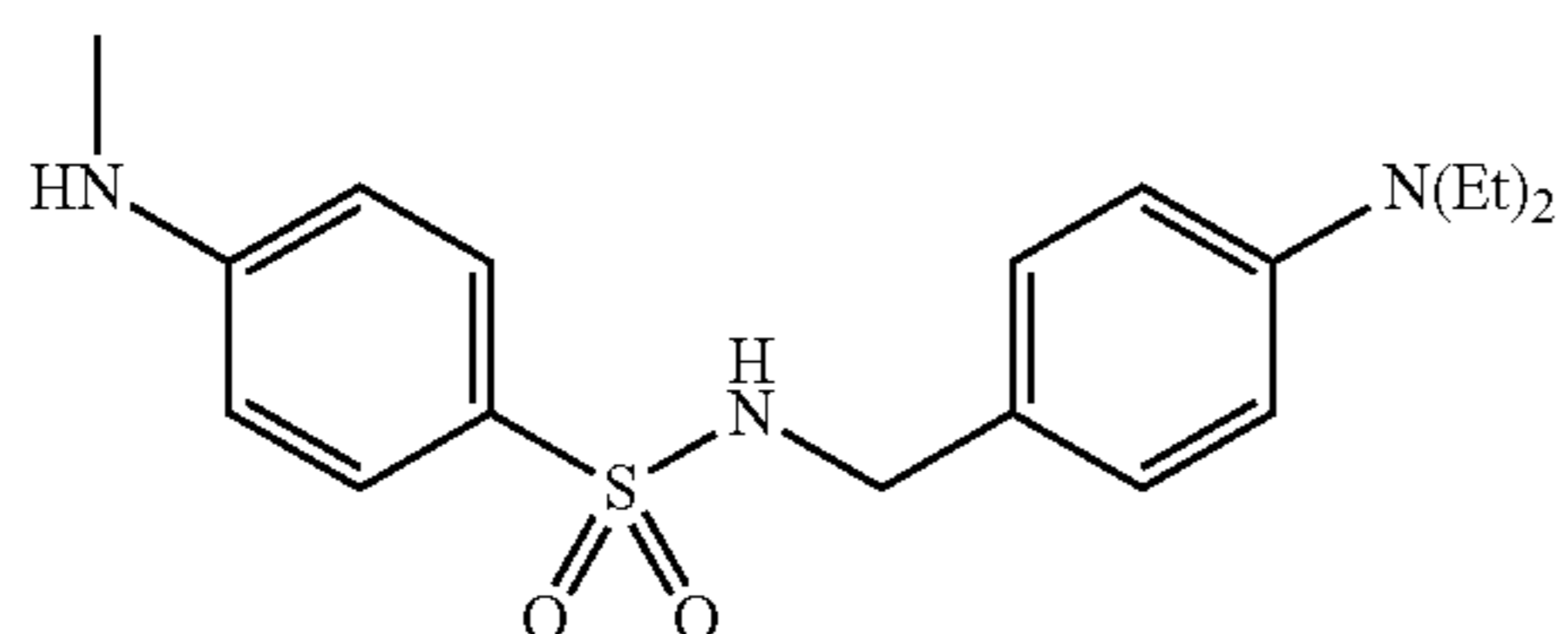
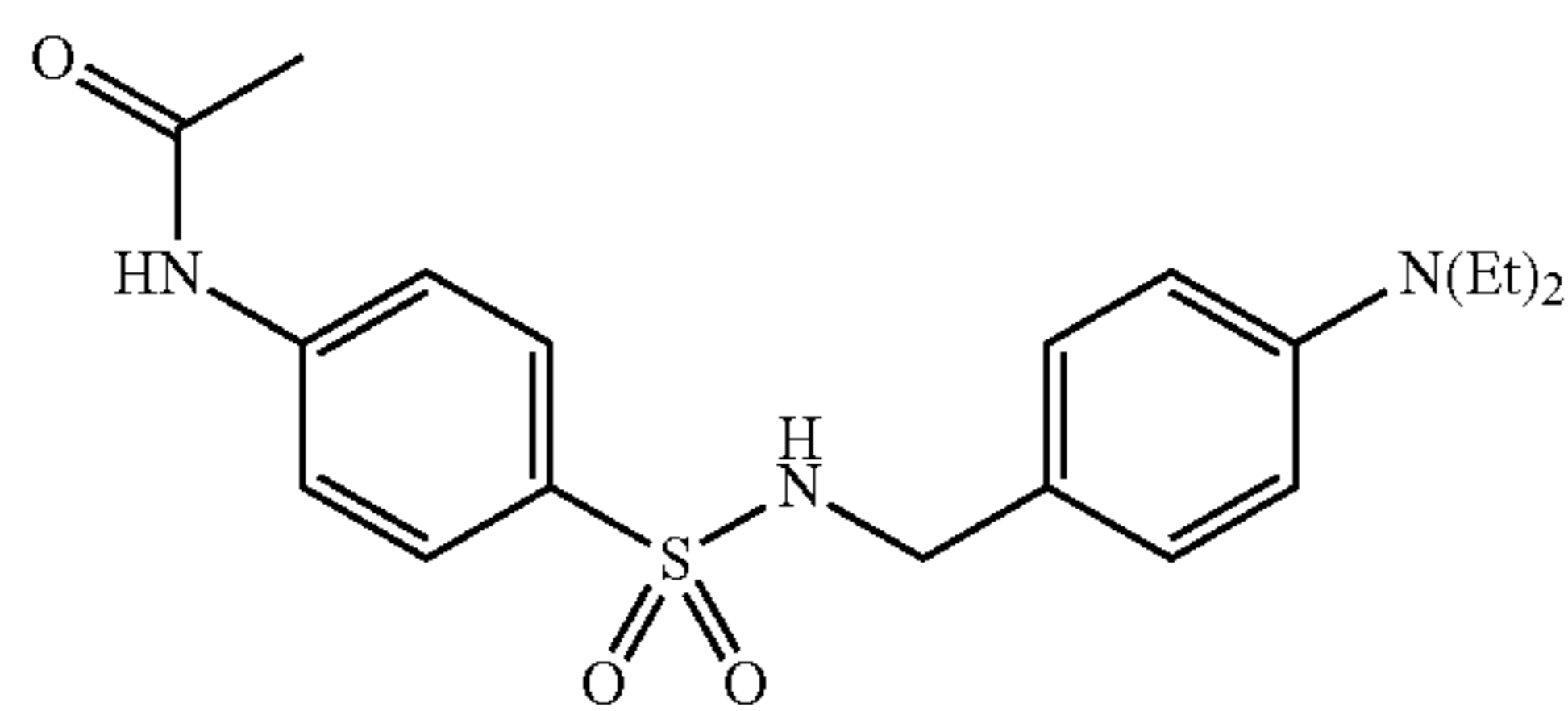
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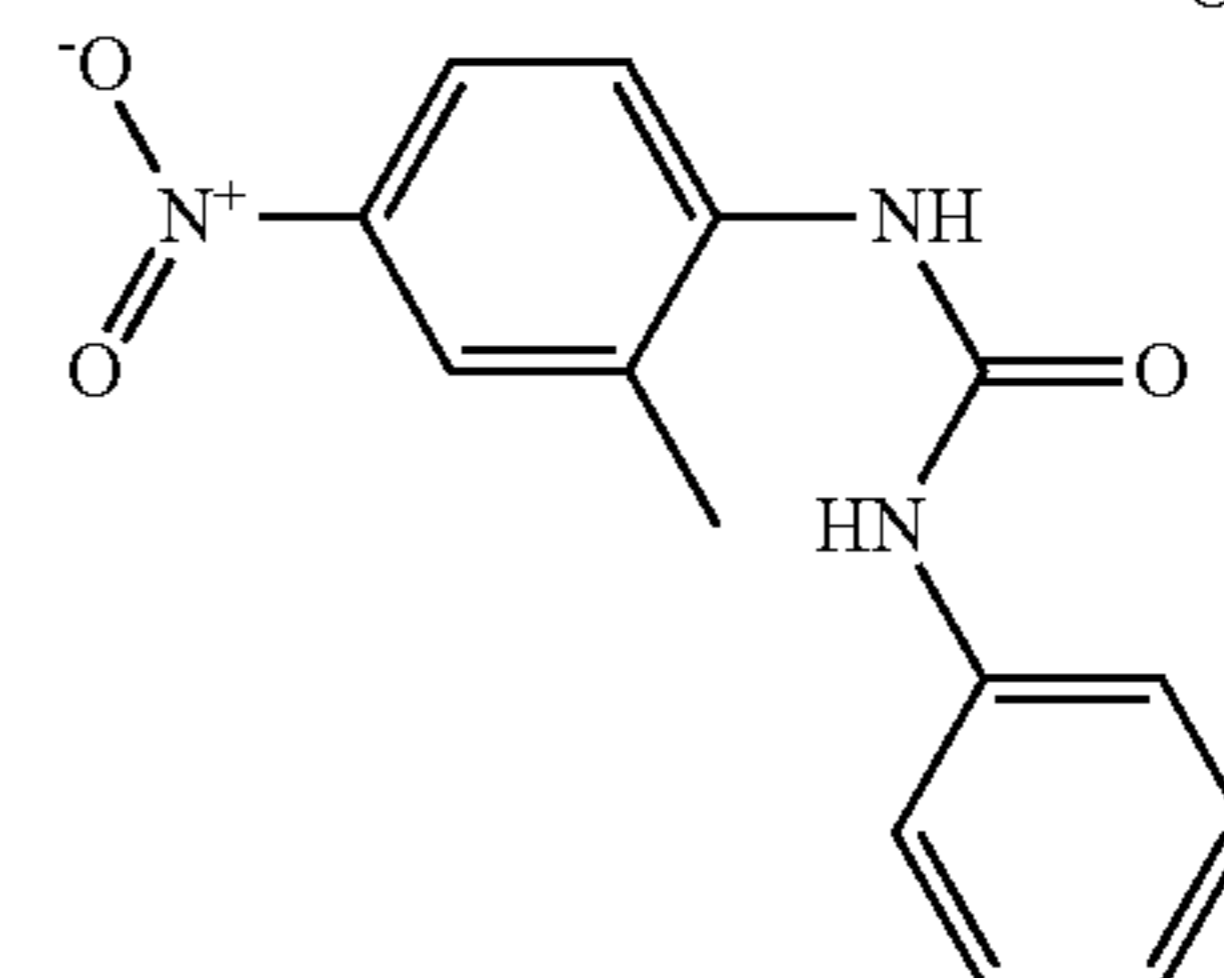
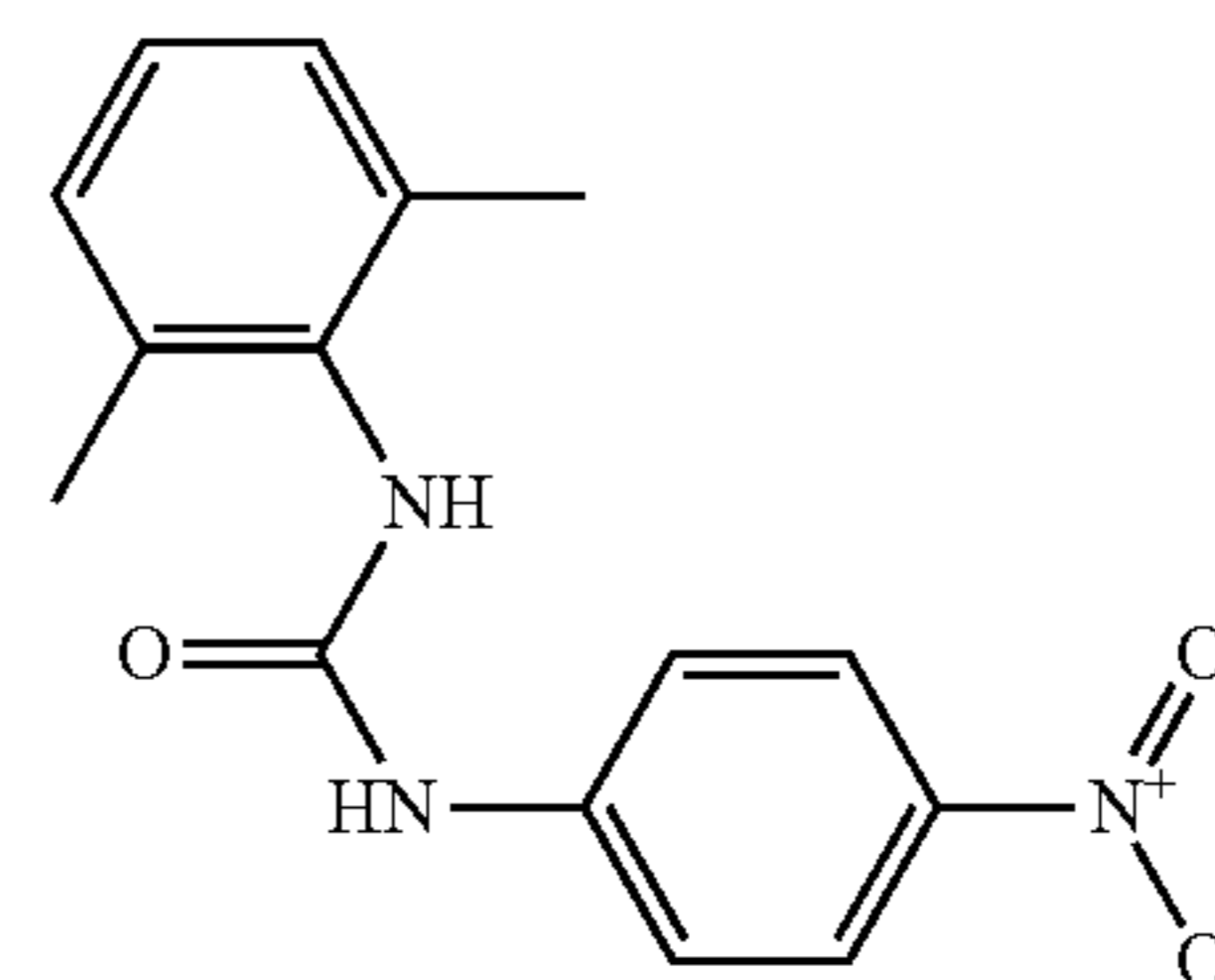
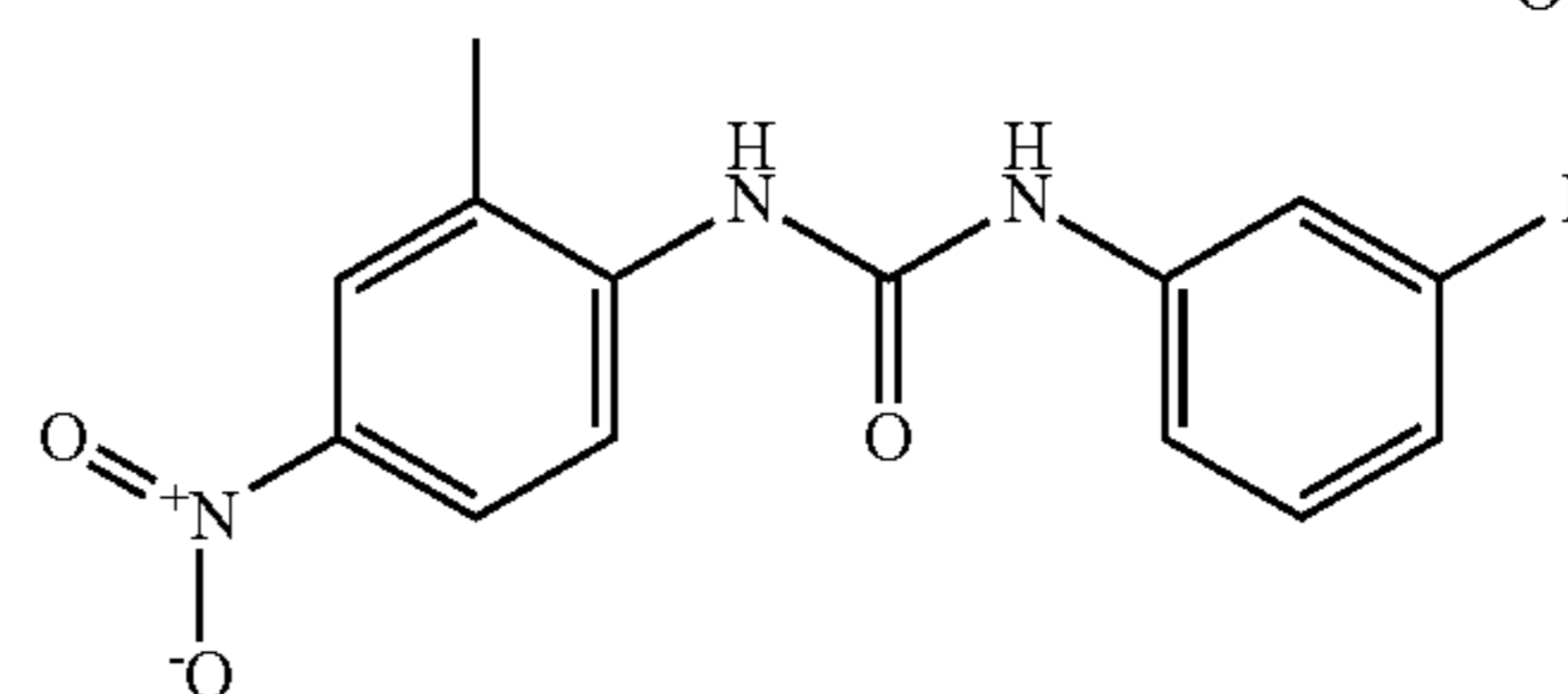
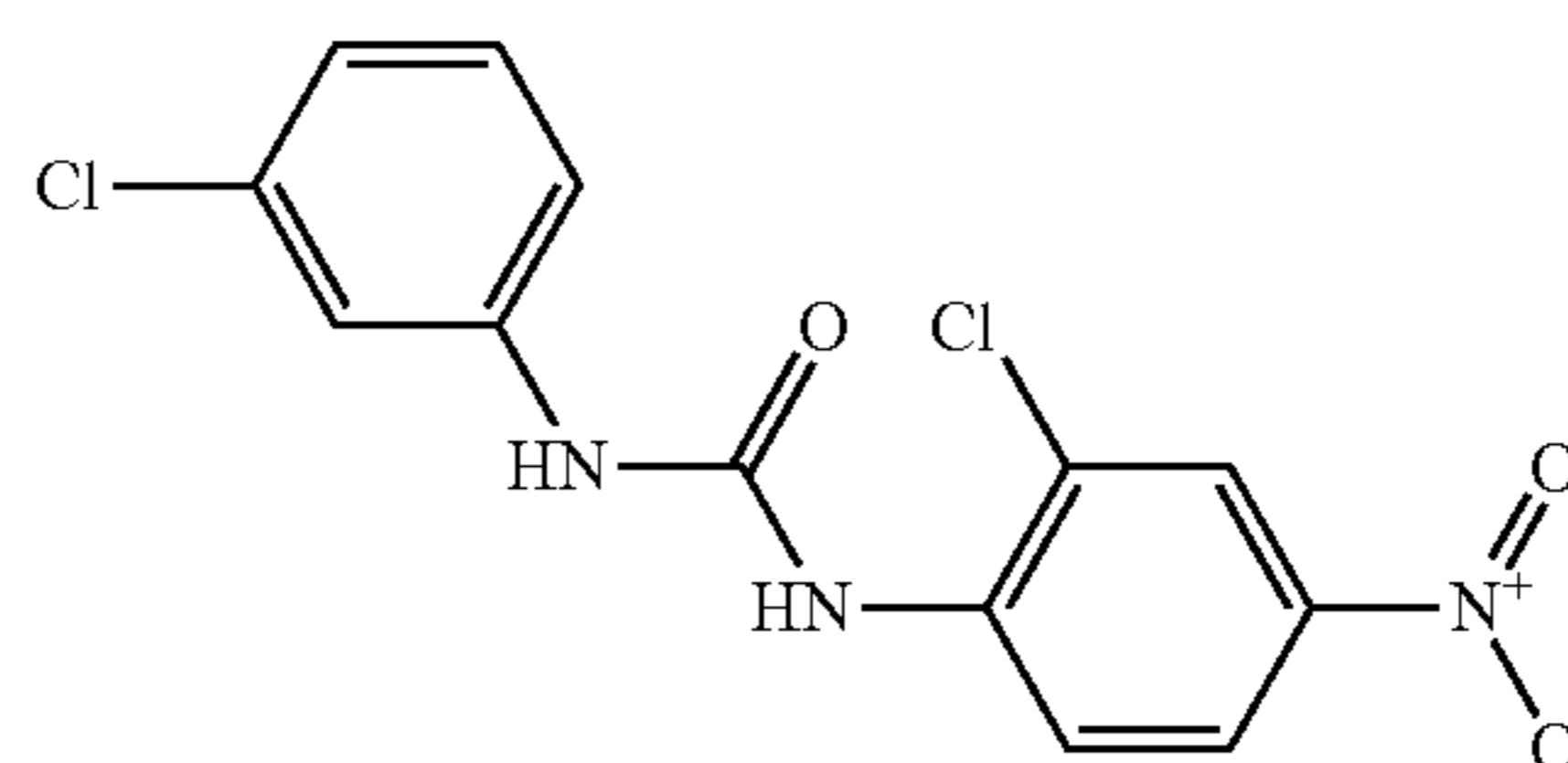
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In some embodiments, the compounds of Formula (I),
Formula (Ia), Formula (Ia'), Formula (Ia''),
Formula (Ia'''), Formula (Ia''''), Formula (Ia'''''),
Formula (Ia''''') do not include the following:

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Methods of Treatment

One aspect of the present technology includes methods of
antagonizing or agonizing hTRPV1 or inhibiting the activity
of TRPV1 in a subject in need thereof, comprising contact-
ing hTRPV1 with a compound or a pharmaceutically accept-
able salt or solvate thereof, or administering a composition
comprising such a compound or a pharmaceutically accept-
able salt or solvate thereof. In some embodiments, the
compound is a diarylurea compound capable of binding to a
space within the TRPV1 molecule comprising (1) an upper
part of the binding pocket formed by several hydrophobic
residues, including Leu518, Leu547, Phe554, Leu663 and
Leu670; (2) a middle consisted of several residues, includ-
ing Tyr511, Met514, Thr550 and Asn551; and (3) a bottom
part mainly formed by two charged residues, Glu570 and
Arg557. In some embodiments, the compound binds with a
K_i value of less than 5 or 4 or 3 or 2 or 1 or 0.5 M. In some
embodiments, the compound is selected from the group
consisting of Formula (I), Formula (Ia), Formula (Ia'),
Formula (Ia''), Formula (Ia'''), Formula (Ia''''), Formula
(Ia'''''), one of Formulae (Ia⁶⁻¹⁰), Formula (Ib), Formula (Ib')
and Formula (Ib''), Formula (Ic), Formula (Id), Formula (Ie),
Formula (II), Formula (IIa), Formula (IIa'), Formula (IIa''),
Formula (IIa'''), Formula (IIa''''), Formula (IIa'''''), and any of
their sub-formulae, or any combination thereof. In one
embodiment the subject is a human.

Some embodiments, include methods of antagonizing or
agonizing hTRPV1 or inhibiting the activity of TRPV1 in a
subject in need thereof and binding to a cannabinoid recep-
tor 2 (CB2) and/or the C-X-C chemokine receptor 2,
"CXCR2," also known as the interleukin 8 receptor beta
(IL8RB), comprising contacting hTRPV1 and one of the

mentioned additional receptors with a compound or a pharmaceutically acceptable salt or solvate thereof, or administering a composition comprising such a compound or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound is a diarylurea compound capable of binding to a space within the TRPV1 molecule comprising (1) an upper part of the binding pocket formed by several hydrophobic residues, including Leu518, Leu547, Phe554, Leu663 and Leu670; (2) a middle consisted of several residues, including Tyr511, Met514, Thr550 and Asn551; and (3) a bottom part mainly formed by two charged residues, Glu570 and Arg557 as well as the CB2 or CXCR2 receptor. In some embodiments, the compound binds with a K_d value of less than 5 or 4 or 3 or 2 or 1 or 0.5 M. In some embodiments, the compound is selected from the group consisting of Formula (I), Formula (Ia), Formula (Ia'), Formula (Ia''), Formula (Ia'''), Formula (Ia''''), Formula (Ia'''''), one of Formulae (Ia⁶⁻¹⁰), Formula (Ib), Formula (Ib') and Formula (Ib''), Formula (Ic), Formula (Id), Formula (e), Formula (II), Formula (IIa), Formula (IIa'), Formula (IIa''), Formula (IIa'''), Formula (IIa''''), Formula (IIa'''''), and any of their sub-formulae, or any combination thereof. In one embodiment the subject is a human.

Other embodiments of the present invention include a method of treating pain associated with transient receptor potential vanilloid type 1 (TRPV1) in a subject in need thereof, comprising administering to the subject an effective amount of a compound or a pharmaceutically acceptable salt or solvate thereof, or administering a composition comprising such a compound or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound is a diarylurea compound capable of binding to a space within the TRPV1 molecule comprising (1) an upper part of the binding pocket formed by several hydrophobic residues, including Leu518, Leu547, Phe554, Leu663 and Leu670; (2) a middle consisted of several residues, including Tyr511, Met514, Thr550 and Asn551; and (3) a bottom part was mainly formed by two charged residues, Glu570 and Arg557, such that the diarylurea compound inhibits activity of TRPV1. In some embodiments, the compound is selected from the group consisting of Formula (I), Formula (Ia), Formula (Ia'), Formula (Ia''), Formula (Ia'''), Formula (Ia''''), Formula (Ia'''''), one of Formulae (Ia⁶⁰), Formula (Ib), Formula (Ib') and Formula (Ib''), Formula (Ic), Formula (Id), Formula (Ie), Formula (II), Formula (IIa), Formula (IIa'), Formula (IIa''), Formula (IIa'''), Formula (IIa''''), Formula (IIa'''''), and any of their sub-formulae, or any combination thereof. In some embodiments, the pain associated with TRPV1 is selected from the group consisting of osteoarthritis, neuropathic pain, migraine, inflammatory bowel disease, and bone cancer pain.

In some embodiments, the method is for the treatment of acute and persistent pain, as well as inflammation, especially for the neuroinflammation. In addition, in some embodiments, the method is for the treatment of auto-immune disorders including neurodegenerative diseases and bone loss.

Compounds of Formulae I and II (including all sub-formulae), or pharmaceutically acceptable salts or solvates thereof, or a composition comprising such a compound or a pharmaceutically acceptable salt or solvate thereof, can be administered to a patient or subject in need of treatment either individually, or in combination with other therapeutic agents that have similar biological activities. For example, Formulae I and II compounds and compositions can be administered as a single dose or as multiple daily doses by a practicing medical practitioner. When combination therapy

is used, however, the compound and the other therapeutic agent can be administered separately at different time intervals, or simultaneously.

Pharmaceutical formulations may include one or more Compounds of Formulae I and/or II (including all sub-formulae), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier. In some embodiments, the composition further comprises, in accordance with accepted practices of pharmaceutical compounding, one or more additional therapeutic agents, pharmaceutically acceptable excipients, diluents, adjuvants, stabilizers, emulsifiers, preservatives, colorants, buffers, and/or flavor imparting agents.

Pharmaceutical Formulations

Pharmaceutical compositions and medicaments may be prepared by mixing one or more compounds of the invention, prodrugs thereof, pharmaceutically acceptable salts or solvates thereof, stereoisomers thereof, tautomers thereof, or solvates thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like to prevent and treat disorders associated with TRPV1 or cannabinoid receptors.

The compounds and compositions of the invention may be used to prepare formulations and medicaments that prevent or treat a variety of disorders associated with TRPV1 or cannabinoid receptors, as described herein. For example, disorders and diseases such as obesity, smoking addiction, cardimetabolic risk factors, and other disorder and diseases associated with the central nervous system can be treated using the methods, compounds, and compositions of the invention. Such compositions can be in any pharmaceutically acceptable form, such as but not limited to in the form of, for example, granules, powders, tablets, capsules, syrup, suppositories, injections, emulsions, elixirs, suspensions or solutions. The compositions can be formulated for any pharmaceutically acceptable route of administration, such as for example, by oral, parenteral, pulmonary, topical, rectal, nasal, vaginal administration, or via implanted reservoir. Parenteral or systemic administration includes, but is not limited to, subcutaneous, intravenous, intraperitoneally, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injections. The following dosage forms are given by way of example and should not be construed as limiting the invention.

Pharmaceutically acceptable salts of the invention compounds are considered within the scope of the present invention. The compounds of the invention have a number of basic nitrogen groups, and as such, pharmaceutically acceptable salts can be formed with inorganic acids (such as hydrochloric acid, hydroboric acid, nitric acid, sulfuric acid, and phosphoric acid), organic acids (e.g. formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, lactic acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, and p-toluenesulfonic acid) or acidic amino acids (such as aspartic acid and glutamic acid). The compounds of the present invention may have acidic substituent groups, and in such cases, it can form salts with metals, such as alkali and earth alkali metals (e.g. Na⁺, Li⁺, K⁺, Ca²⁺, Mg²⁺, Zn²⁺), organic amines (e.g. ammonia, trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine) or basic amino acids (e.g. arginine, lysine and ornithine).

Certain compounds within the scope of the invention are derivatives referred to as prodrugs. The expression "prodrug" denotes a derivative of a known direct acting drug, e.g. esters and amides, which derivative has enhanced delivery characteristics and therapeutic value as compared to the

drug, and is transformed into the active drug by an enzymatic or chemical process; see Notari, R. E., "Theory and Practice of Prodrug Kinetics," *Methods in Enzymology*, 112: 309-23 (1985); Bodor, N., "Novel Approaches in Prodrug Design," *Drugs of the Future*, 6: 165-82 (1981); and Bundgaard, H., "Design of Prodrugs: Bioreversible-Derivatives for Various Functional Groups and Chemical Entities," in DESIGN OF PRODRUGS (H. Bundgaard, ed.), Elsevier (1985), and Goodman and Gilman, *The Pharmacological Basis Of Therapeutics*, 8th ed., McGraw-Hill (1992).

For oral, buccal, and sublingual administration, powders, suspensions, granules, tablets, pills, capsules, gencaps, and caplets are acceptable as solid dosage forms. These can be prepared, for example, by mixing one or more compounds of the present invention, or pharmaceutically acceptable salts or tautomers thereof, with at least one additive such as a starch or other additive. Suitable additives include any pharmaceutically acceptable excipient, including but not limited to sucrose, lactose, cellulose sugar, mannitol, maltitol, dextran, starch, agar, alginates, chitins, chitosans, pectins, tragacanth gum, gum arabic, gelatins, collagens, casein, albumin, synthetic or semi-synthetic polymers or glycerides. Optionally, oral dosage forms can comprise other ingredients to aid in administration, such as an inactive diluent, or lubricants such as magnesium stearate, or preservatives such as paraben or sorbic acid, or anti-oxidants such as ascorbic acid, tocopherol or cysteine, a disintegrating agent, binders, thickeners, buffers, sweeteners, flavoring agents or perfuming agents. Tablets and pills may be further treated with suitable coating materials known in the art.

Definitions

It is noted that, as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

As used herein, the term "about" will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

By "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be incorporated into a pharmaceutical composition administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the composition in which it is contained. When the term "pharmaceutically acceptable" is used to refer to a pharmaceutical carrier or excipient, it is implied that the carrier or excipient has met the required standards of toxicological and manufacturing testing or that it is included on the Inactive Ingredient Guide prepared by the U.S. and Drug administration.

By "patient" is meant any animal for which treatment is desirable. Patients may be mammals, and typically, as used herein, a patient is a human individual.

The term "pharmaceutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds of the present invention which are water or oil-soluble or dispersible; which are suitable for treatment of

diseases without undue toxicity, irritation, and allergic-response; which are commensurate with a reasonable benefit/risk ratio; and which are effective for their intended use. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylsulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, paratoluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds of the present invention can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form pharmaceutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion.

Hence, the present invention contemplates sodium, potassium, magnesium, and calcium salts of the compounds of the present invention and the like.

The term "solvates" is used in its broadest sense. For example, the term solvates includes hydrates formed when a compound of the present invention contains one or more bound water molecules.

Certain ranges are presented herein with numerical values being preceded by the term "about". The term "about" is used herein to provide literal support for the exact number that it precedes, as well as a number that is near to or approximately the number that the term precedes. In determining whether a number is near to or approximately a specifically recited number, the near or approximating unrecited number may be a number which, in the context in which it is presented, provides the substantial equivalent of the specifically recited number.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, representative illustrative methods and materials are now described.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges and are also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits,

ranges excluding either or both of those included limits are also included in the invention.

This invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

Working Examples

The present technology is further illustrated by the following examples, which should not be construed as limiting in any way.

Binding Competition Assay and Ca²⁺ Uptake Assay. Materials.

[³H]Resiniferatoxin ([³H]RTX, 37 Ci/mmol) was provided by Perkin Elmer Life Sciences (Boston, Mass.). Radioactive calcium (Ca-45, specific activity 5-30 Ci/g) was obtained from Perkin Elmer. Nonradioactive RTX was obtained from LC laboratories (Waltham, Mass.). Capsaicin was provided by Sigma-Aldrich (St. Louis, Mo.).

Stable hTRPV1 Expression Cell Line Subculture.

Tet-On induced CHO-hTRPV1 cells were cultured in maintaining medium (F12 supplemented with 10% TET-free FBS [Atlanta Biologicals, GA], 25 mM HEPES, 10 µg/ml blasticidin and 250 µg/ml geneticin (all from Invitrogen Life Sciences; Grand Island, N.Y.). TRPV1 protein was induced with induction medium (F12 supplemented with 10% FBS, 25 mM HEPES, and 1 µg/ml tetracycline) as described below for ligand binding and Ca uptake measurements.

RTX Competition Binding Assay.

Binding studies with [³H]RTX were carried out as follows. The binding assay mixtures were prepared in 1.5 ml centrifuge tubes and consisted of a fixed concentration (approximately 2 nM) of [³H]RTX (37 Ci/mmol specific activity, PerkinElmer Life Sciences), various concentrations of competing ligands, and 100 µg protein of membranes from induced CHO-hTRPV1 expressing cells (approximately 1-3×10⁶ cells) in Dulbecco's phosphate buffered saline (DPBS, with Ca²⁺ & Mg²⁺) for a total volume of 350 µl. The assay mix contained bovine serum albumin at a final concentration of 0.25 mg/ml (Cohn fraction V; Sigma-Aldrich, St. Louis, Mo.). In each set of experiments, nonspecific binding were determined in the presence of 200 nM non-

radioactive RTX. The binding reaction was initiated by placing the assay mixture in a 37° C. shaking water bath for 60 minutes (-30 rpm). The assay mixture was then chilled on ice for 2-3 min before adding 100 µl of α₁-acid glycoprotein (2 mg/ml; Sigma-Aldrich) and mixed thoroughly. The tubes were kept on ice for an additional 10 min. The bound and free ligands were then separated by centrifugation (12,200 rpm for 15 minutes) in a Beckman Coulter centrifuge Allegra 21R. 200 µl of supernatant was collected for determination of free ligand. The remainder was removed by aspiration. The bottom portion of the tubes containing the membranes was cut off and bound radioactivity determined. Radioactivity was measured by scintillation counting. Data were analyzed using GraphPad Prism. K_i values for compounds were determined by competition for binding of [³H]RTX to the hTRPV1 and represent the mean SEM of triplicate binding curves. In each curve, triplicate determinations were performed at each ligand concentration.

Calcium Uptake Assays.

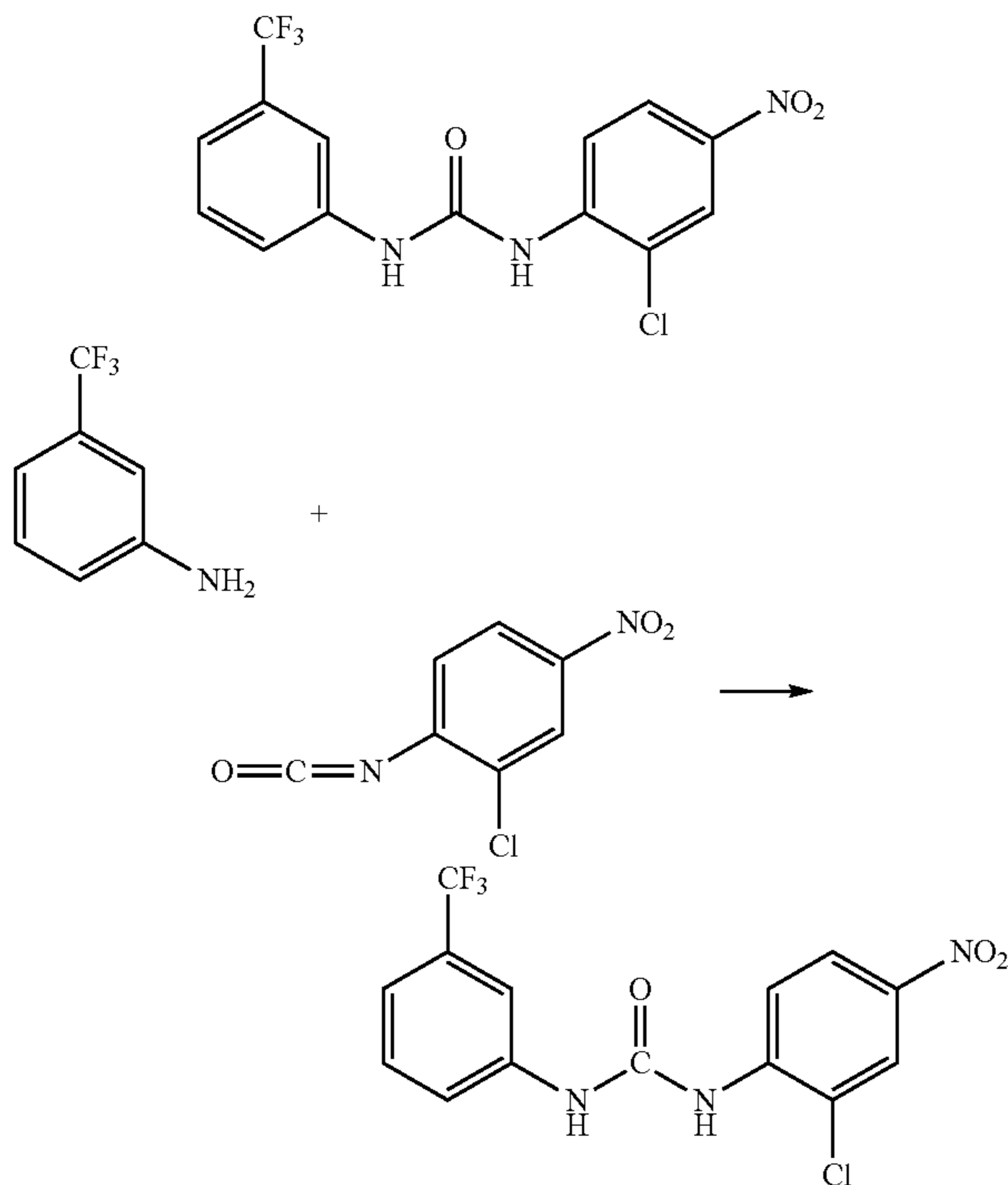
CHO-hTRPV1 cells were plated in 24-well plates, reaching 40 to 60% confluence in maintaining medium after 24 hours. The cells were washed once with Dulbecco's phosphate buffered saline (DPBS; Invitrogen, Grand Island, N.Y.) to remove antibiotics, and fresh medium with tetracycline (inducing medium) was added to induce TRPV1 expression. Experiments were done approximately 24 hours after induction. The cells were at least 90% confluent at the time of the assays.

For agonist Ca²⁺ uptake assays, the inducing medium was aspirated and replaced by DMEM (supplemented with bovine serum albumin (0.25 mg/mL), Ca²⁺ (37 kBq/mL), and 100 µl of increasing concentrations of the non-radioactive ligand for a total volume of 400 µl/well. The cells were incubated for 5 min in a water bath at 37° C. For uptake measurements by a full agonist, a saturating concentration of capsaicin (3000 nM) was used as a positive control. Immediately after incubation, the assay medium was aspirated and the cells were washed twice with ice cold DPBS (no Ca²⁺ & Mg²⁺). The cells were then lysed in radioimmunoprecipitation assay buffer (50 mM Tris-Cl pH 7.5, 150 mM NaCl, 1% Triton X-100, 1% SDS, and 1% sodium deoxycholate; 400 µL/well) for at least 40 min on a shaker. Aliquots (300 µL) of the cell lysates were counted in a liquid scintillation counter. Background uptake was determined in the absence of either compound or capsaicin. For the antagonism assays, capsaicin (30 nM) was included along with increasing concentrations of the ligand being evaluated. The cells were incubated for 5 min in a water bath at 37° C. Immediately after incubation, the assay medium was aspirated and the cells were washed twice with ice-cold DPBS (no Ca²⁺ & Mg²⁺). The cells were then lysed in radioimmunoprecipitation assay buffer for at least 40 min on a shaker. Aliquots of the cell lysate were counted in a liquid scintillation counter. Triplicate points at each concentration of ligand were determined in each experiment. Compounds were initially screened at a concentration of 30 M. Compounds showing greater than 10% agonism/antagonism were evaluated in triplicate experiments. As indicated, full dose response curves for compounds showing activity were performed at least three times. Data was analyzed using GraphPad Prism.

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Example 1. Synthesis of Compound 1

The purpose of this example is to synthesize Compound 1, the structure of which is shown below:

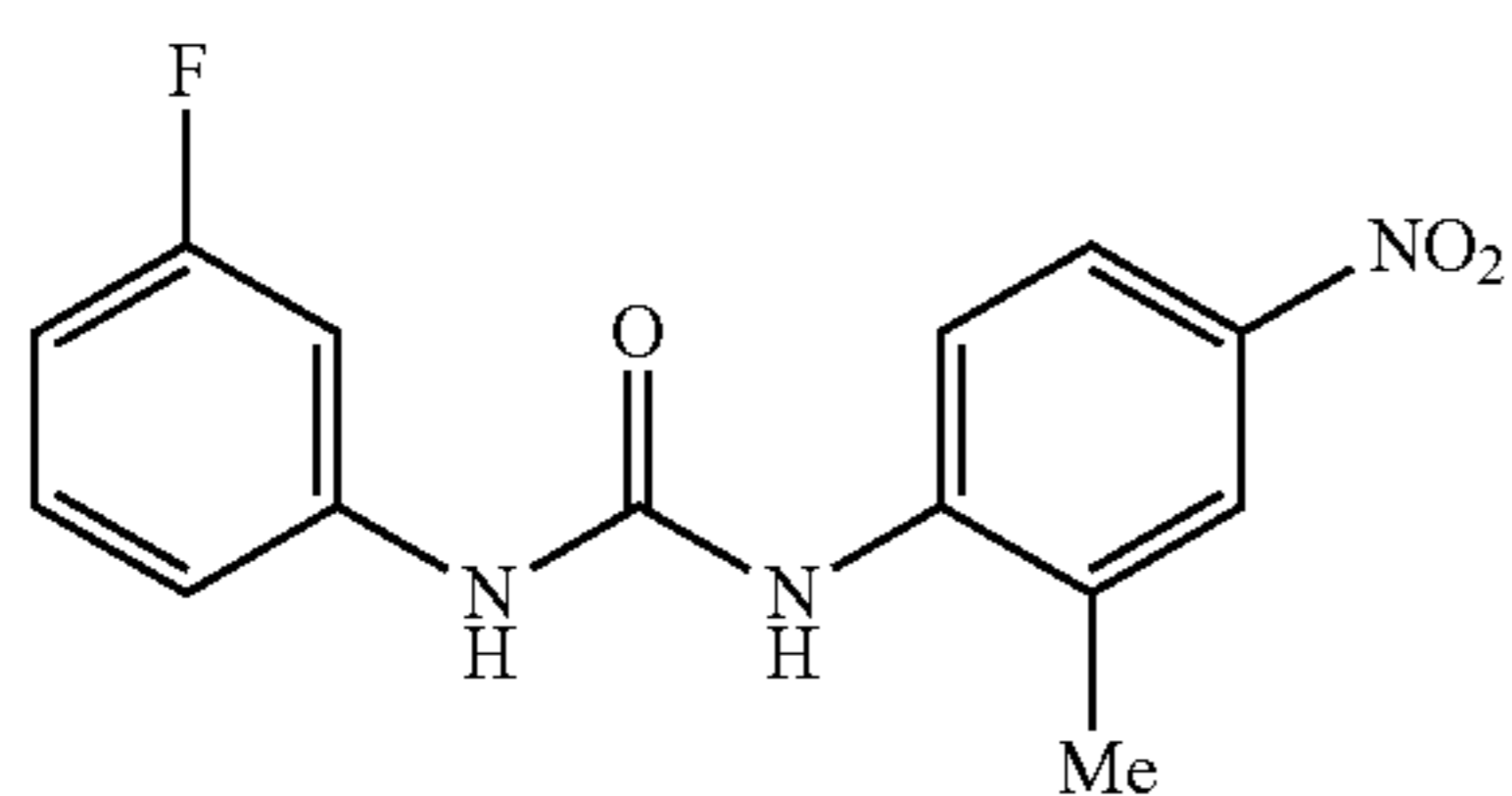


Taking 2-chloro-1-isocyanato-4-nitrobenzene and 3-(trifluoromethyl)aniline as starting materials, compound 1 was synthesized using the same method as compound 2.

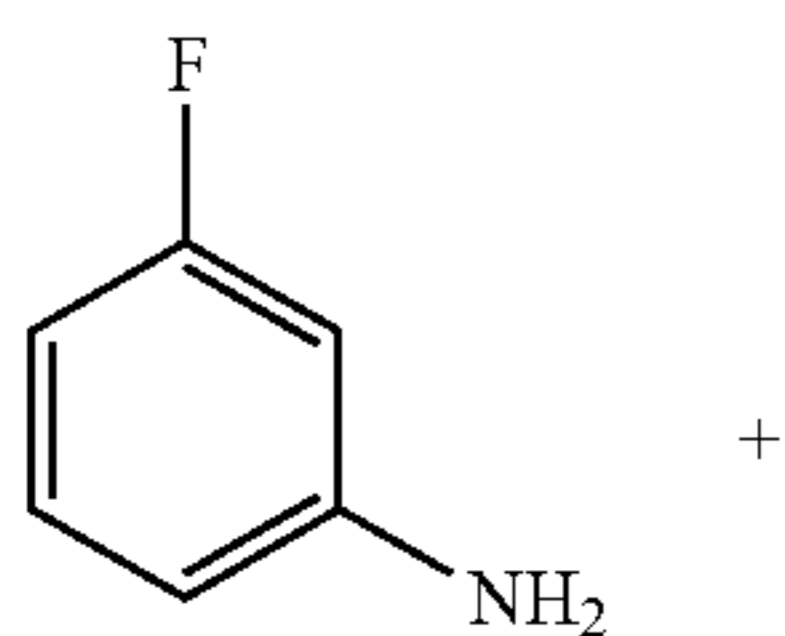
This compound yielded K_i values for capsaicin antagonism of $2.60 \pm 0.62 \mu\text{M}$. It likewise inhibited $[3\text{H}]\text{RTX}$ binding to hTRPV1 with K_i value of $1.11 \pm 0.21 \mu\text{M}$.

Example 2. Synthesis of Compound 2

The purpose of this example is to synthesize Compound 2, the structure of which is shown below:

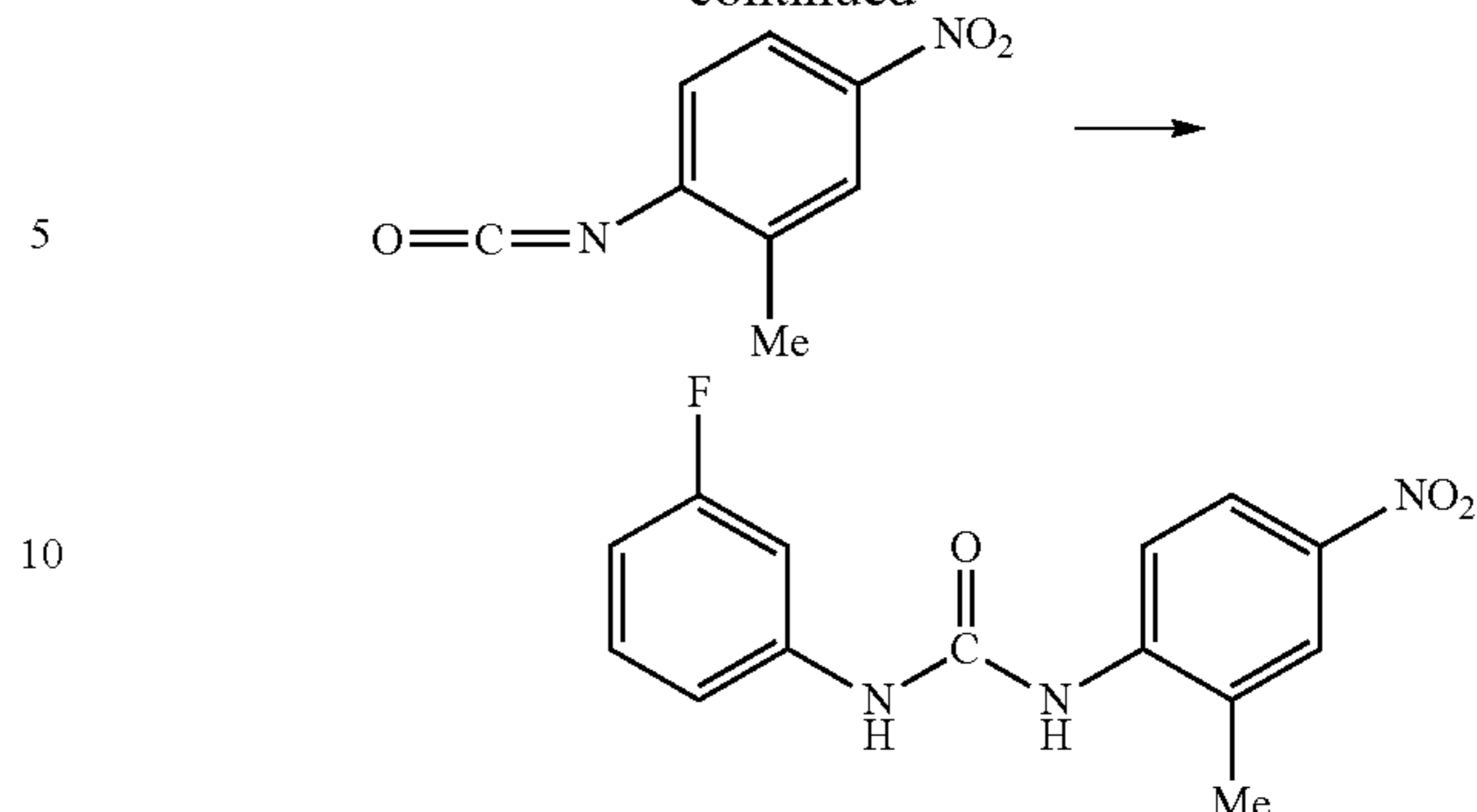


Compound 2 was synthesized by the method of the following Scheme.



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-continued

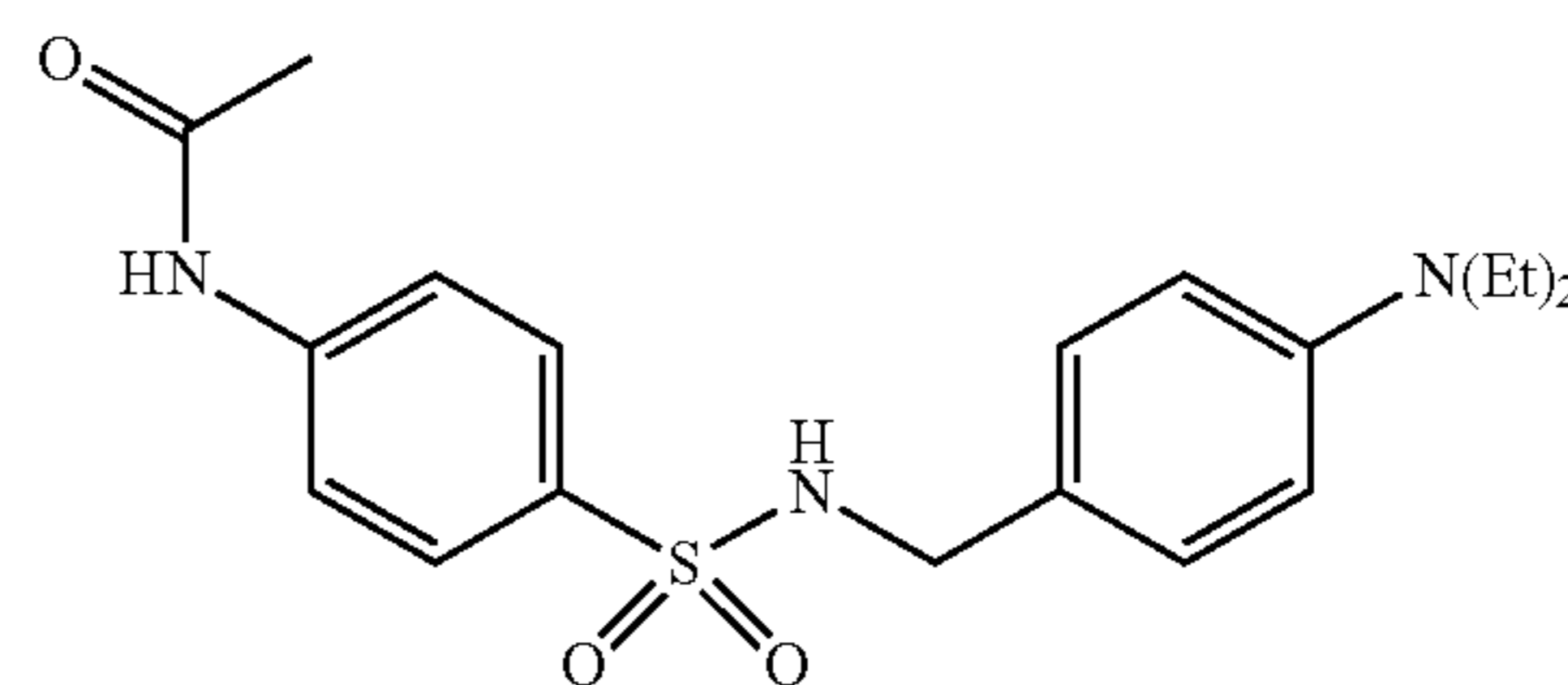


General procedure of coupling reaction between isocyanate and amine.

1-isocyanato-2-methyl-4-nitrobenzene (1.6 mmol, 1 eqv.) was dissolved in dichloromethane (10 mL). 3-fluoroaniline (2.4 mmol, 1.5 eqv) was added, followed by triethylamine (3.6 mmol, 2.25 eqv) and the resulting mixture was stirred overnight at room temperature. A precipitate was formed, filtered and washed with dichloromethane. The solid particles were purified with flash column chromatography utilizing ethyl acetate/petroleum ether (1:2). The target compound was obtained as off-white solid (100 mg, yield: 34%). ^1H NMR (400 MHz, DMSO- d_6 , ppm) δ 9.60 (s, 1H), 8.44 (s, 1H), 8.34 (d, $J=8.80$ Hz, 1H), 8.14-8.08 (m, 2H), 7.54 (d, $J=11.60$ Hz, 1H), 7.37-7.35 (m, 1H), 7.15-7.13 (m, 1H), 6.86-6.85 (m, 1H), 2.38 (s, 3H). LC-MS (ESI, m/z): 290.0 ($\text{M}+\text{H}$) $^+$. This compound yielded K_i values for capsaicin antagonism of 4.50 ± 0.88 M. It likewise inhibited $[3\text{H}]\text{RTX}$ binding to hTRPV1 with K_i value of $5.20 \pm 0.32 \mu\text{M}$.

Example 3. Synthesis of Compound 3

The purpose of this example is to synthesize Compound 3, the structure of which is shown below:



4-Acetamidobenzene-1-sulfonyl chloride (466 mg, 2.0 mmol) and 4-(aminomethyl)-N,N-diethylaniline (356 mg, 2.0 mmol) were dissolved in 10 mL of water and 5 mL of dimethylformamide. The mixture was added K_2CO_3 (414 mg, 3.0 mmol) and stirred at room temperature for 12 h. The precipitated solid was filtered, washed with water, and dried in vacuo to obtain the crude product, which was recrystallized in ethanol to prepare the final compound N-(4-(N-(4-(diethylamino)benzyl)sulfonyl)phenyl)acetamide (453 mg, 60%).

^1H NMR (400 MHz, DMSO- d_6) δ 10.28 (s, 1H), 7.69-7.75 (m, 5H), 6.97 (d, $J=8.4$ Hz, 2H), 6.52 (d, $J=8.4$ Hz, 2H), 3.79 (d, $J=6.0$ Hz, 2H), 3.28-3.35 (m, 4H), 2.09 (s, 3H), 1.05 (t, $J=6.8$ Hz, 6H). LC-MS (ESI): m/z 376.1 ($\text{M}+\text{H}$) $^+$. It antagonized capsaicin stimulation of hTRPV1 by $12.7 \pm 1.0\%$ at 30 M.

Example 4. The Sequence Alignment Between hTRPV1 and rTRPV1

The purpose of this example was to determine the sequence alignment between human TRPV1 (hTRPV1) and rat TRPV1 (rTRPV1), as shown in FIG. 1.

The whole sequence identity between hTRPV1 and rTRPV1 was 85.7%. We used the structure of rTRPV1-capsaicin (PDB entry: 3J5R, EM resolution: 4.2 Å) to construct the 3D structures of hTRPV1. The intact sequence of hTRPV1 (Q8NER1, 839 residues for one monomer) was downloaded from the UniProtKB/Swiss-Prot (<http://www.uniprot.org/uniprot/>).

We truncated some residues before Leu112 for the N terminus and some residues after Lys719 for the C terminus. We also truncated 24 residues from Asn604 to Ser627. This truncation was necessary because the corresponding residues were unsolved in the structures of rTRPV1. Therefore, the generated sequence was from Leu112 to Lys603 and from Tyr628 to Lys719 (584 residues for one monomer). We connected Lys603 and Tyr628 to generate a continuous polypeptide sequence. We then aligned the sequence and built the homology model based on this hTRPV1 sequence by using our reported protocol.

Example 5. Ramachandran Plots of hTRPV1 Model

The purpose of this example was to generate Ramachandran plots of hTRPV1.

Ramachandran plots of hTRPV1 model constructed by rTRPV1. 95.5% (554/580) of all residues were in favored regions. 99.1% (575/580) of all residues were in allowed regions. There were 5 outliers (ϕ , ψ): Glu250 (56.0, -24.3), Leu385 (88.0, 72.8), Thr407 (88.0, -19.7), Asp459 (22.4, -126.2), Pro462 (-28.9, -68.7).

After obtaining the 3D structures, SYBYL-X 1.3 was used for the energy minimizations. SYBYL-X 1.3, Tripos International, 1699 South Hanley Rd., St. Louis, Mo., 63144, USA. 2010. ProSA-web Z-scores and ProCheck Ramachandran plots were used for structural stereochemical evaluation of the hTRPV1 models.

Example 6. Detailed Binding Modes of Six Antagonists with hTRPV1

The purpose of this example was to determine detailed binding modes of six antagonists with hTRPV1.

Most residues involved in the binding pocket had similar roles for the recognition of antagonists. (1) Ser512 (not shown), Arg557, and Glu570 formed a hydrophilic pocket that interacted with the polar/charged groups of the antagonists. (2) Thr550 and/or Tyr511 also formed strong hydrogen

bonds with these 8 compounds. (3) Several hydrophobic residues formed strong hydrophobic interactions with all these antagonists, including Met514, Leu515 (not shown), Leu518, Leu547, Ala666 (not shown), and Leu670. The agonists and antagonists therefore shared the same binding pocket and similar binding interactions, which were congruent with the findings of GPCRs.

Example 7. Determination of Four Allosteric Binding Pockets in Tetramer hTRPV1 Model

The purpose of this example was to determine four allosteric binding pockets in a tetramer hTRPV1 model.

Each predicted binding pocket was formed by five trans-membrane domains from two adjacent monomers, including S3, S4, S4-S5 linker, S5, and S6. An important observation was that the binding pockets of hTRPV1 differed from the traditional orthosteric binding site because they were exposed to the lipids. Our MD simulation showed that both AMG9810 (antagonist) and RTX (agonist) were close to the lipid molecules (~5.4 Å and 5.7 Å for these two compounds, respectively). All the results showed that these were allosteric binding pockets. Our findings were congruent with the reports by Julius and co-workers. Liao, M.; Cao, E.; Julius, D.; Cheng, Y. Structure of the TRPV1 Ion Channel Determined by Electron Cryo-Microscopy. *Nature* 2013, 504, 107-112. In their apo structure of rTRPV1, they observed some density in the same site as the agonists, possibly corresponding to a detergent molecule or lipid. They suggested that this binding site of ligands was in exchange with lipid molecules. This hypothesis was supported by experimental data, suggesting that TRPV1 can be activated by lipophilic or lipid molecules, such as diacylglycerols and anandamide. Consistently, some studies already showed a shared binding site for RTX and anandamide and partial activation of TRPV1 by diacylglycerol.

Example 8. In Vitro Testing of Compound

For an initial evaluation of the utility of the model for identifying novel structures with hTRPV1 activity, a panel of several in-house compounds was examined. The in-house compounds were selected on the basis of the docking score (higher than 8.0). Of all the in-house compounds, one (XIE1-203Y) antagonized capsaicin stimulation of hTRPV1 by $12.7 \pm 1.0\%$ at 30 M. Among the other compounds, 2 gave $98.2 \pm 2.7\%$ (compound 1) and $79.9 \pm 4.9\%$ (compound 2) inhibition at 30 M. These compounds yielded K_i values for capsaicin antagonism of 2.60 ± 0.62 (compound 1) and 4.50 ± 0.88 (compound 2) M, respectively. They likewise inhibited [^3H]RTX binding to hTRPV1 with K_i values of 1.11 ± 0.21 and 5.20 ± 0.32 μM , respectively.

TABLE 1

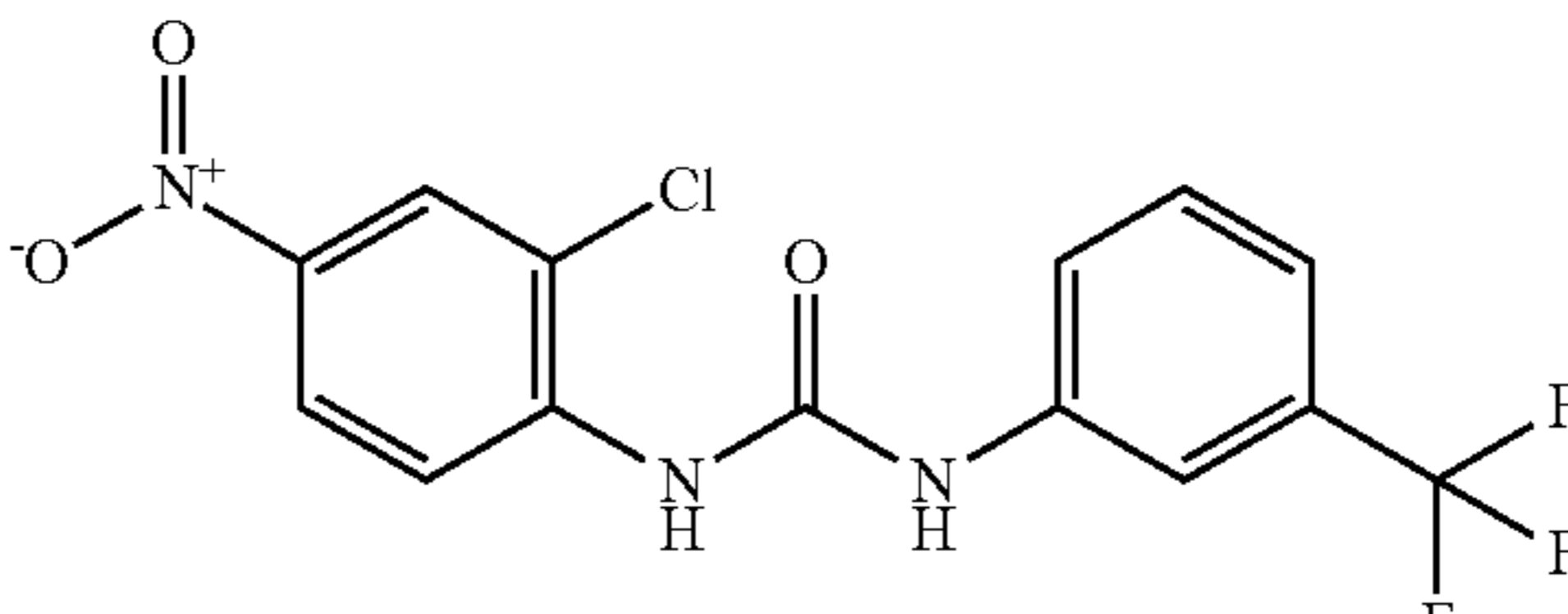
TRPV1 inhibitors.				
Compound ID	Structure	LogP	MW	K_i (μM) (or % inhibition at 30 μM)
1		4.09	359.68	2.57 ± 0.62 ($92.2 \pm 2.7\%$)

TABLE 1-continued

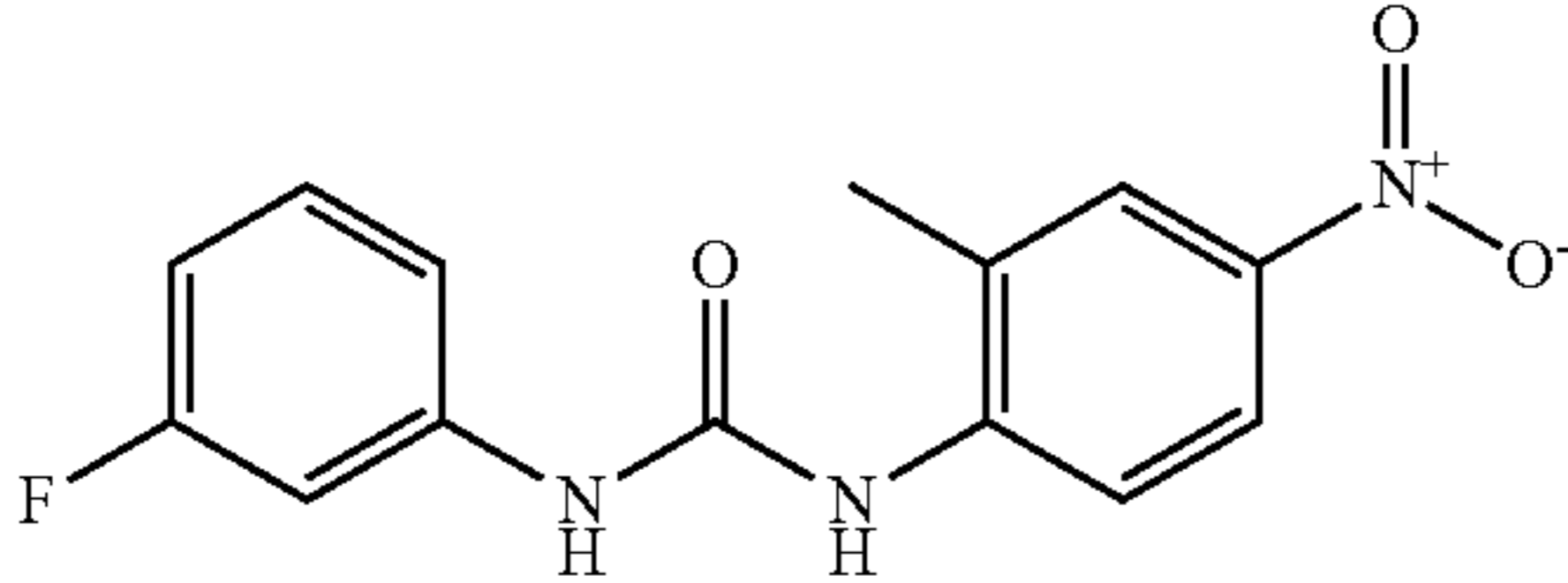
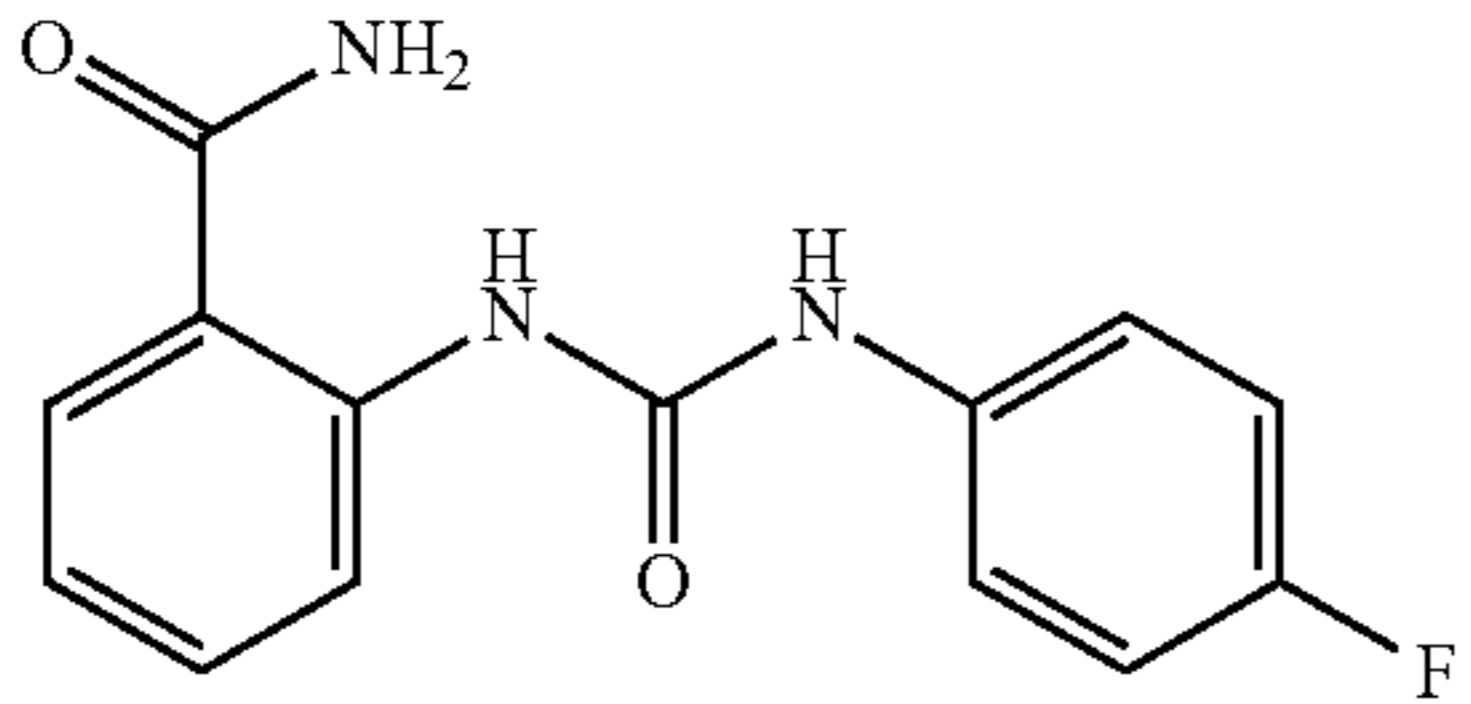
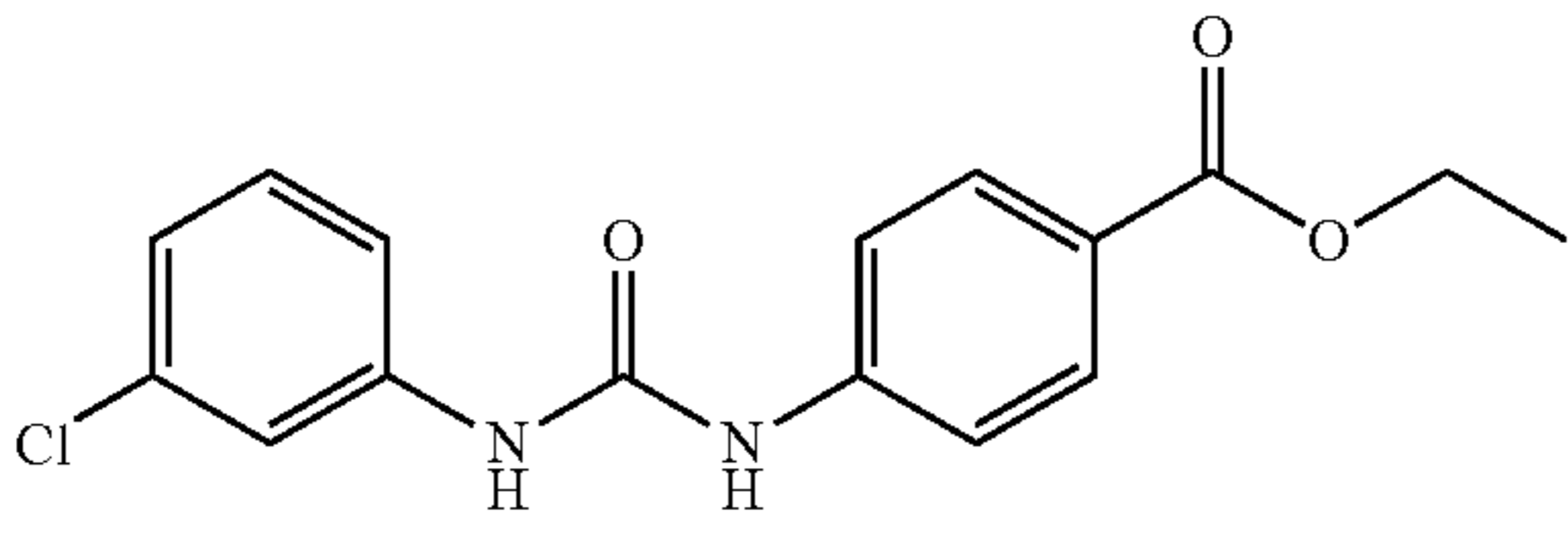
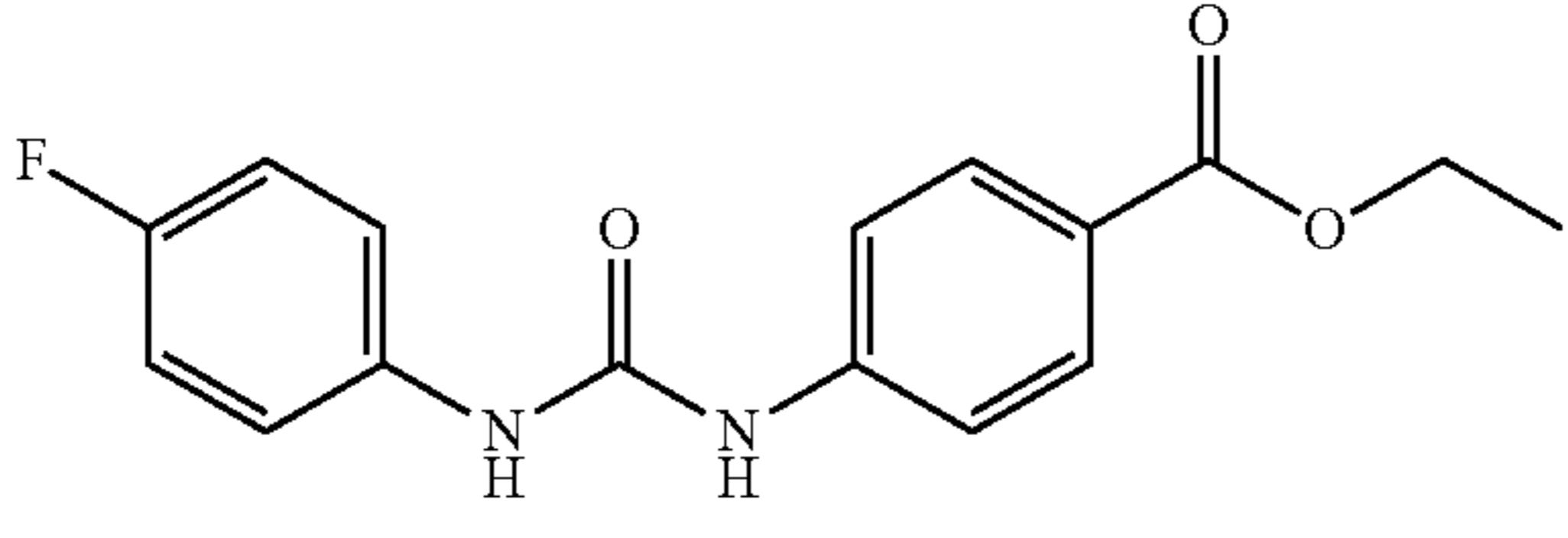
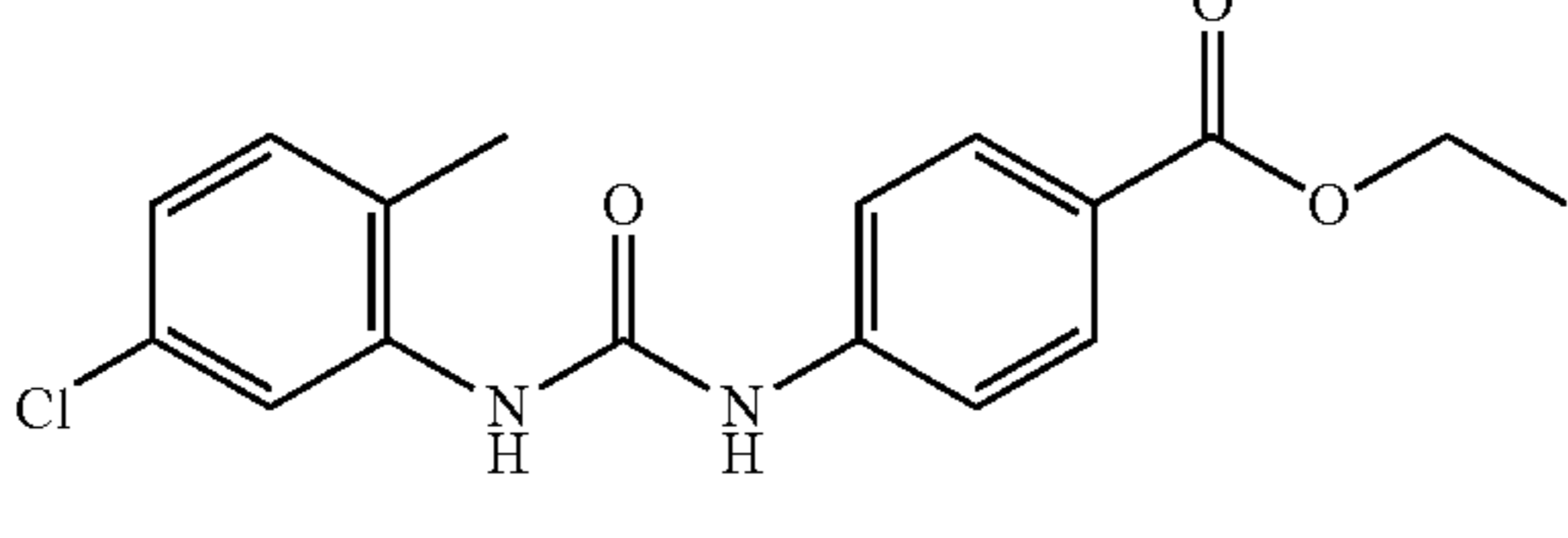
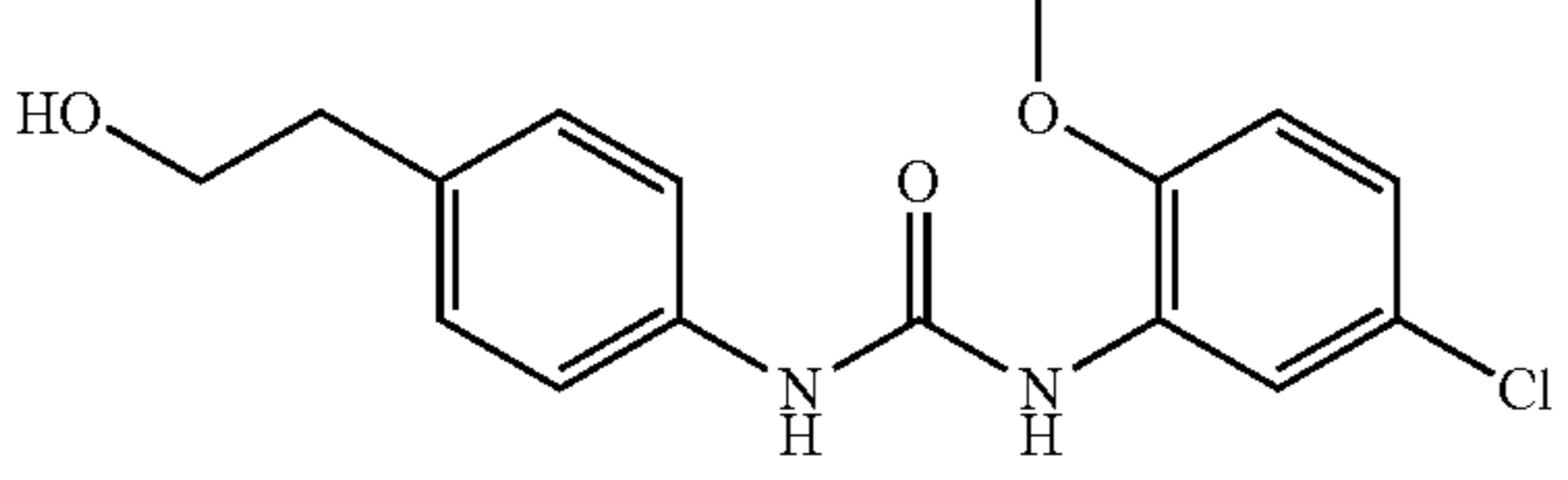
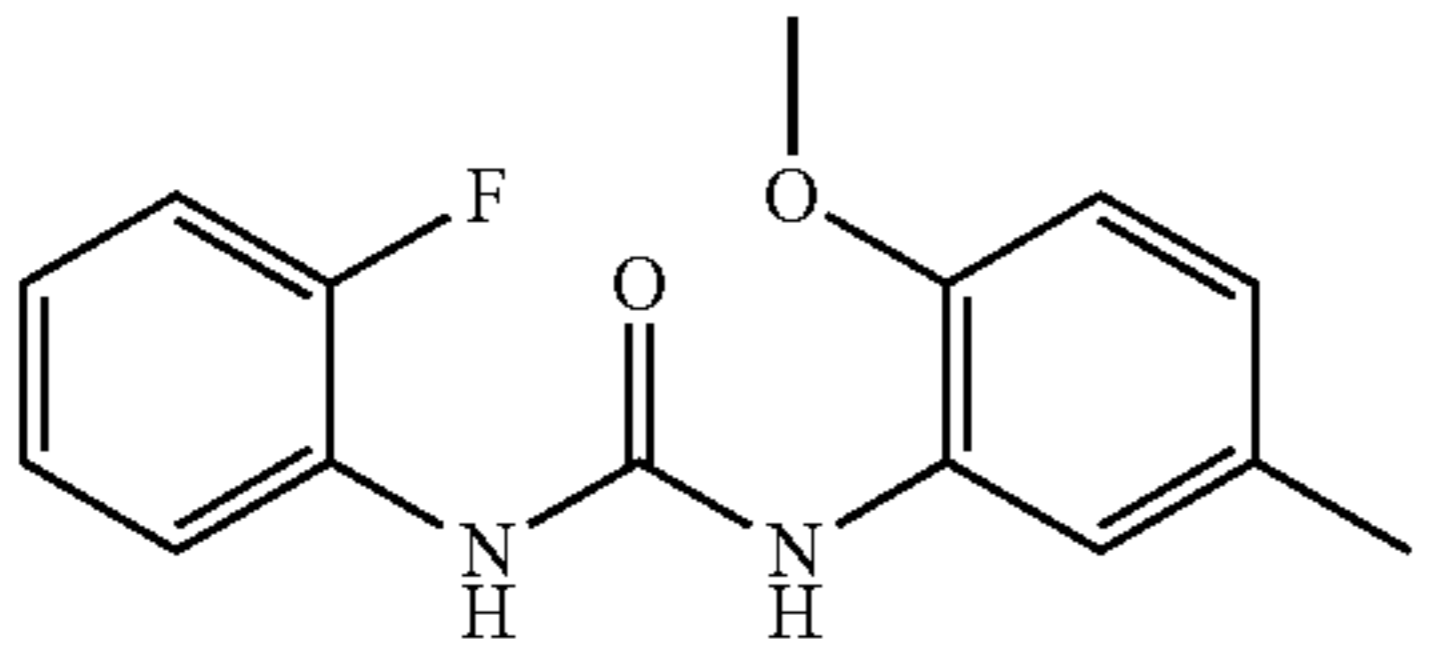
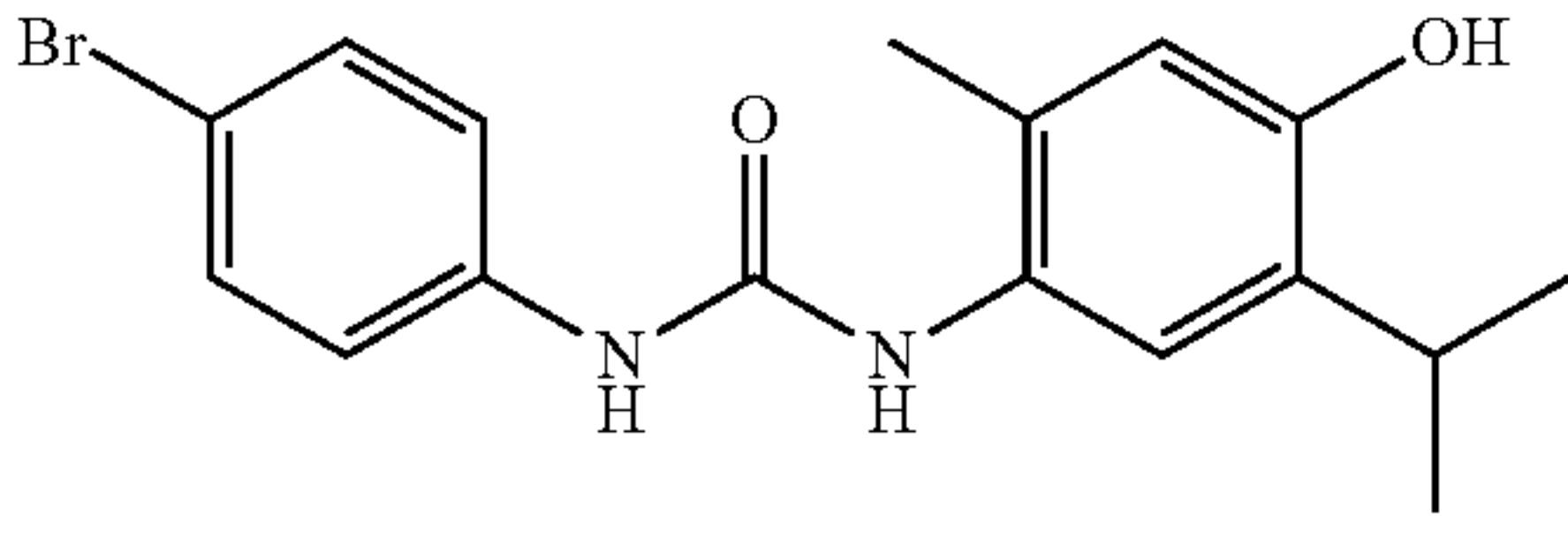
TRPV1 inhibitors.				aK_i (μM) (or % inhibition at 30 μM)
Compound ID	Structure	LogP	MW	
2		3.04	289.27	4.52 ± 0.88 ($79.9 \pm 4.9\%$)
3		1.58	273.27	$32 \pm 8\%$
4		3.23	318.76	11.7 ± 1.3 ($64.5 \pm 7.3\%$)
5 ^b		2.83	302.31	2.84 ± 0.21^b ($55.7 \pm 7.8\%$ agonism)
6		3.72	332.78	$34 \pm 7\%$
7		2.65	320.77	$33 \pm 7\%$
8		3.03	274.30	$28 \pm 6\%$
9		4.67	363.26	$27 \pm 14\%$

TABLE 1-continued

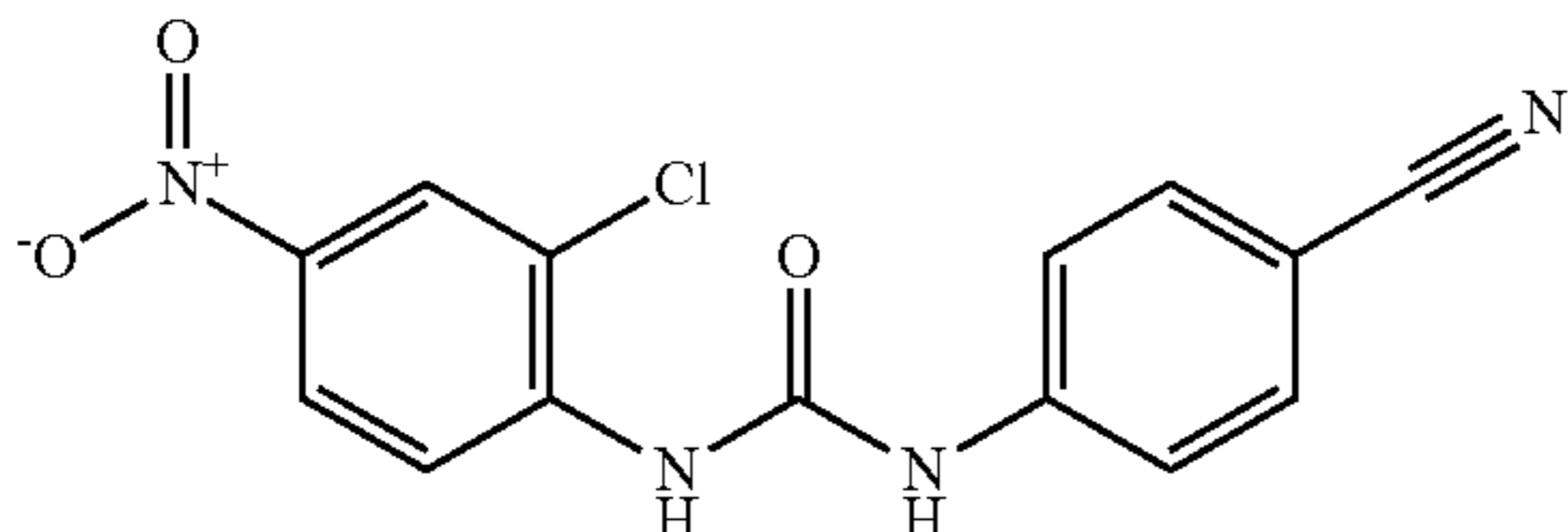
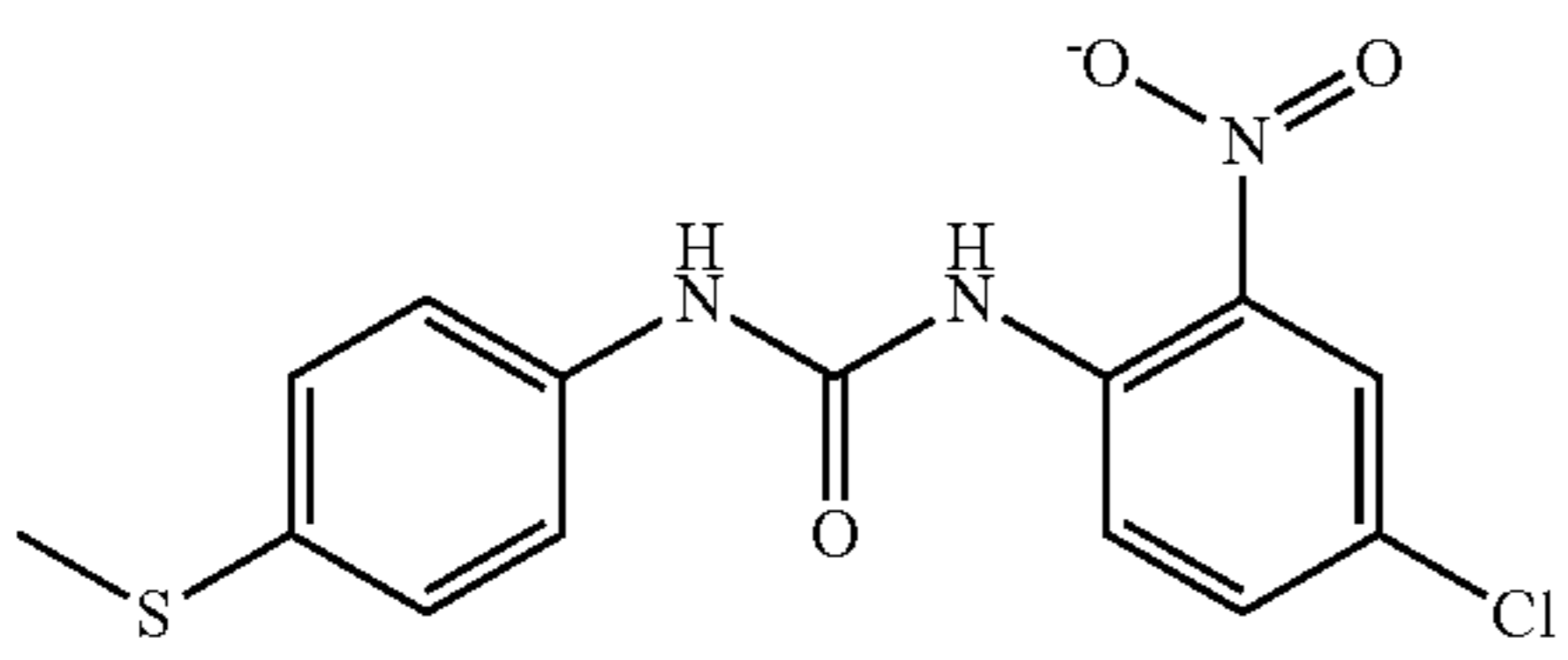
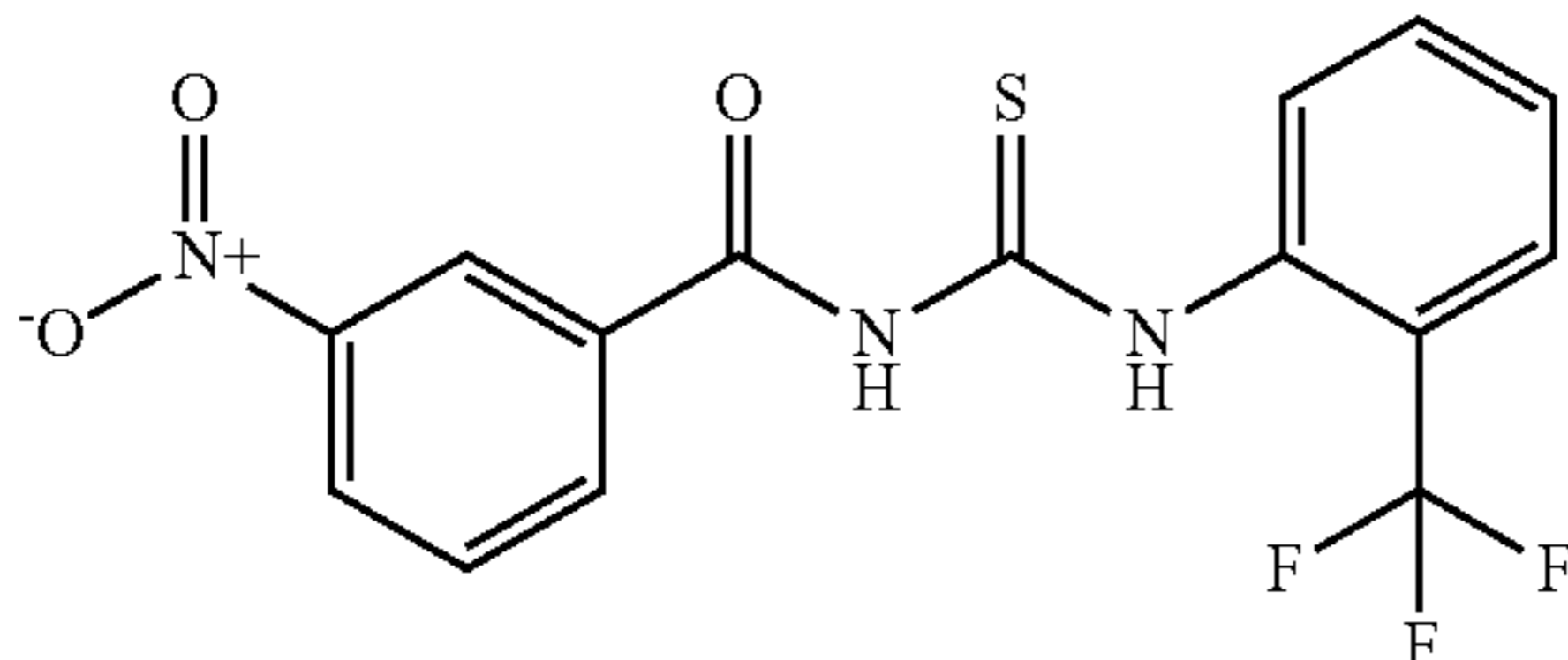
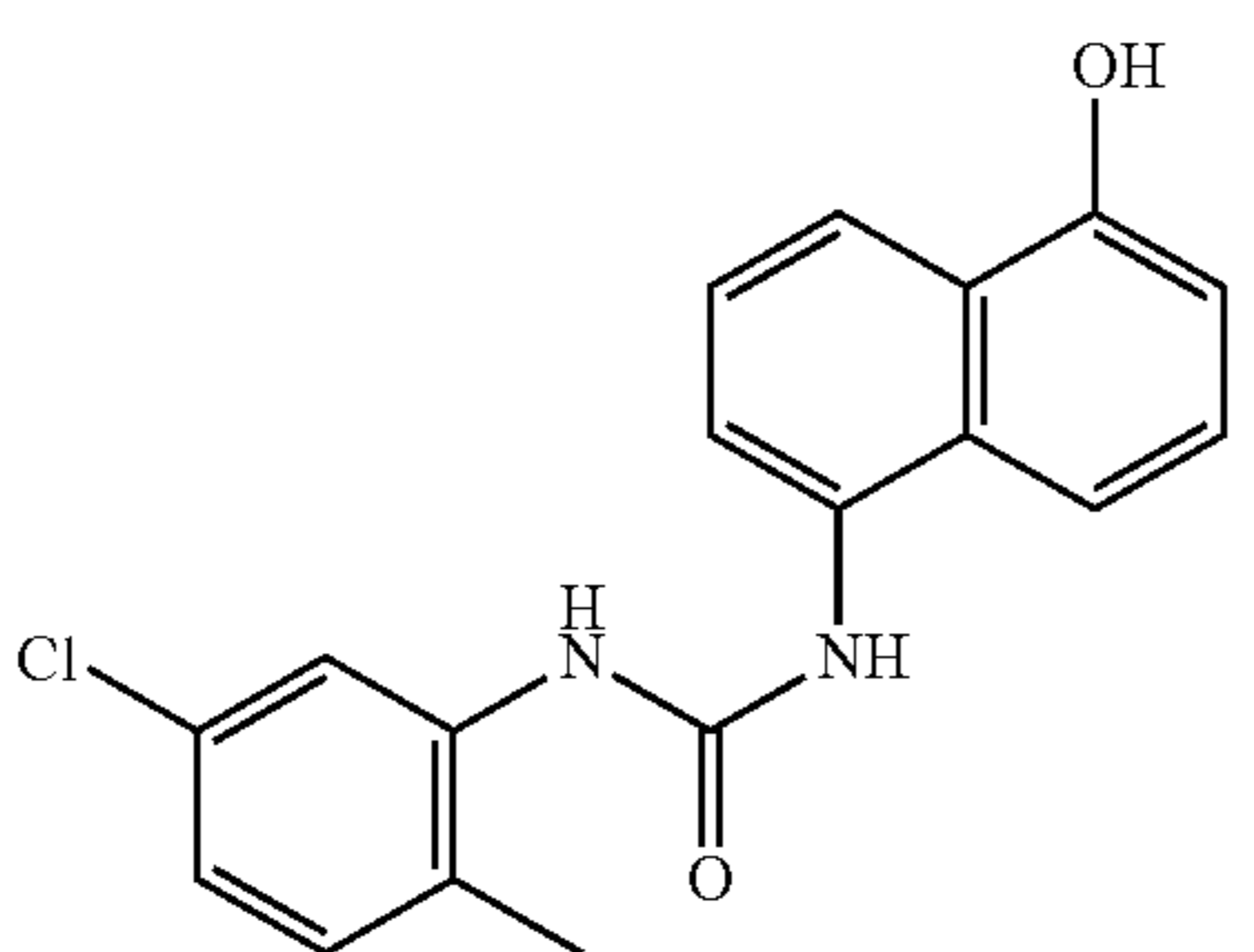
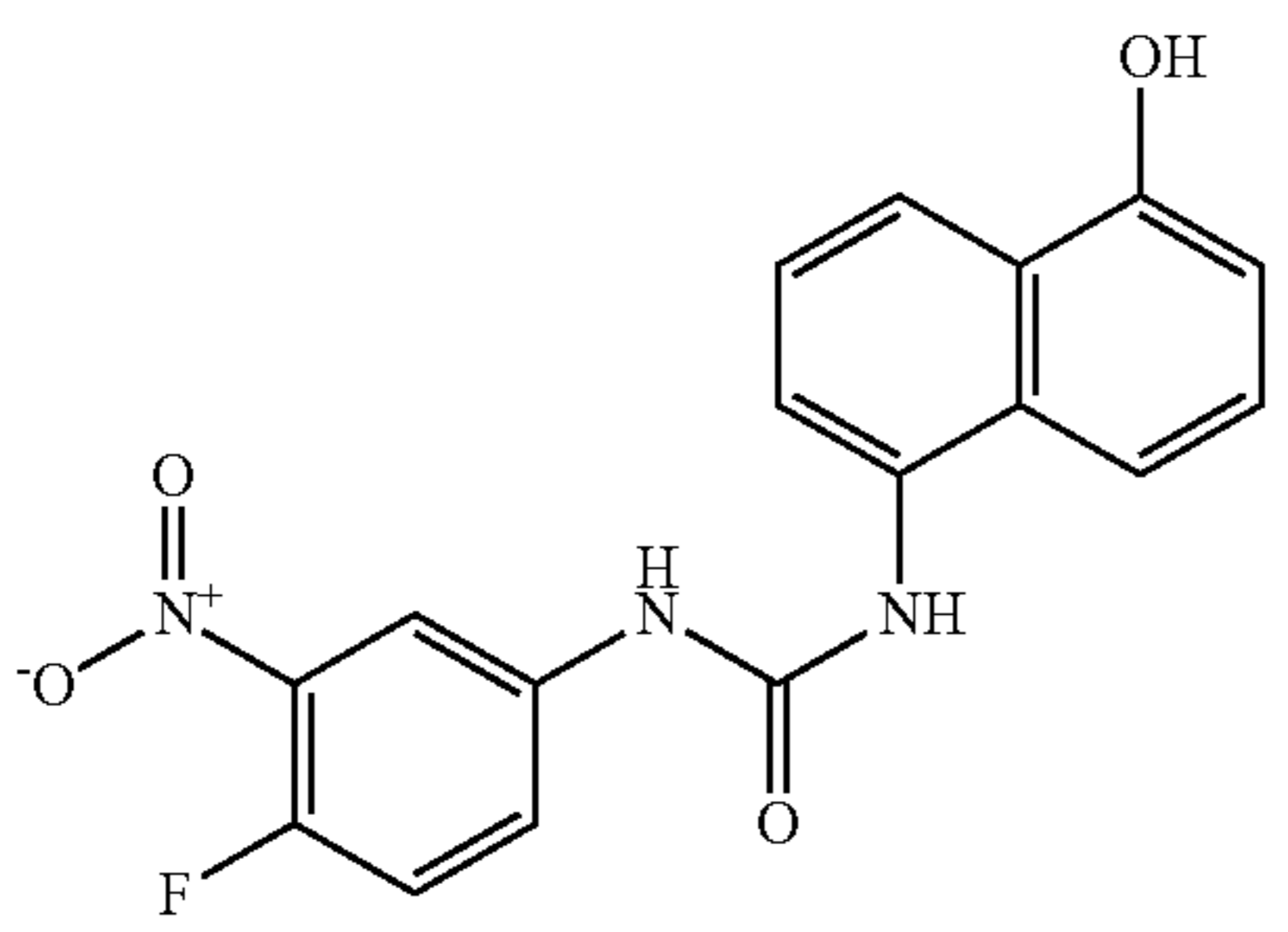
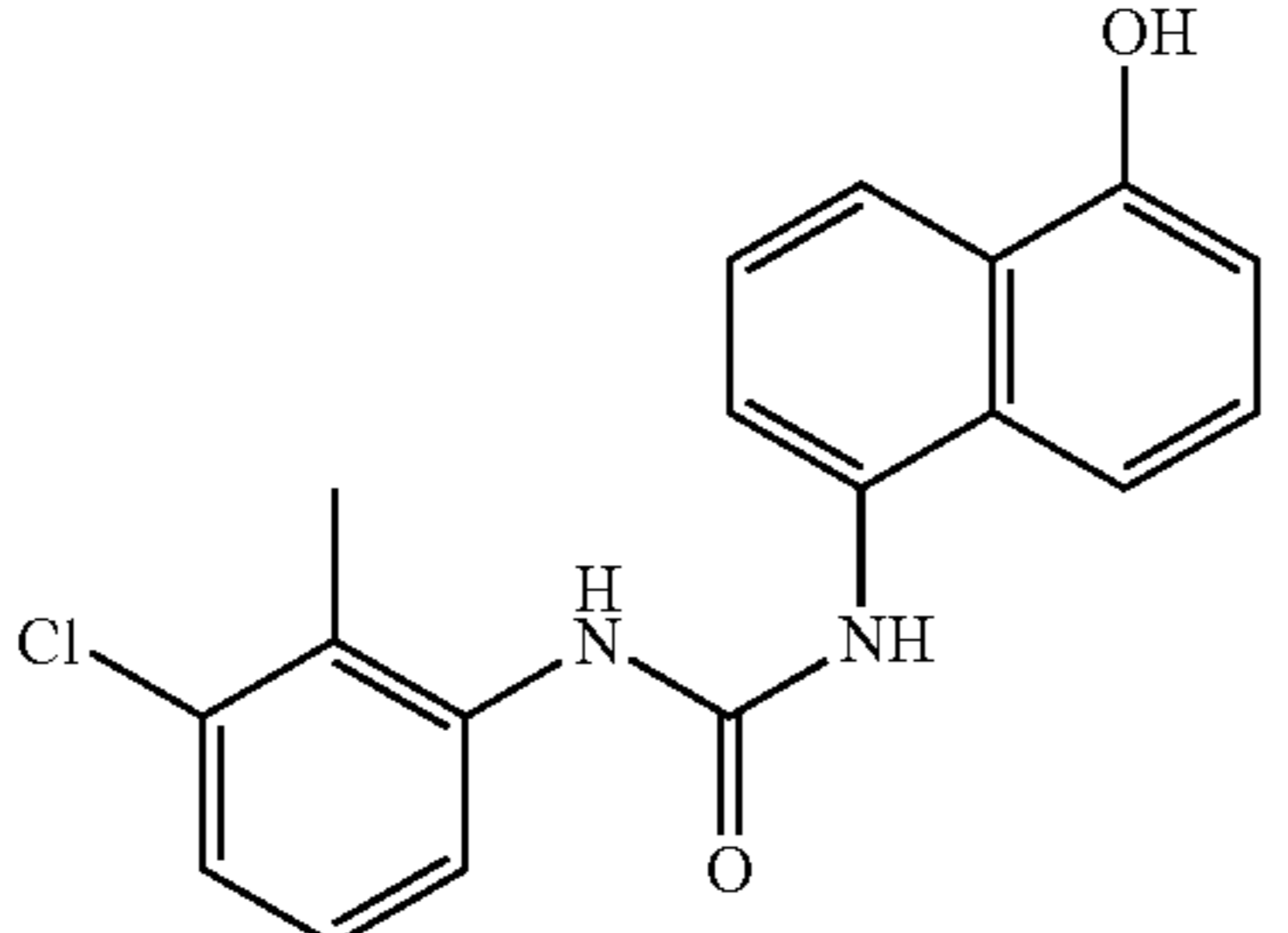
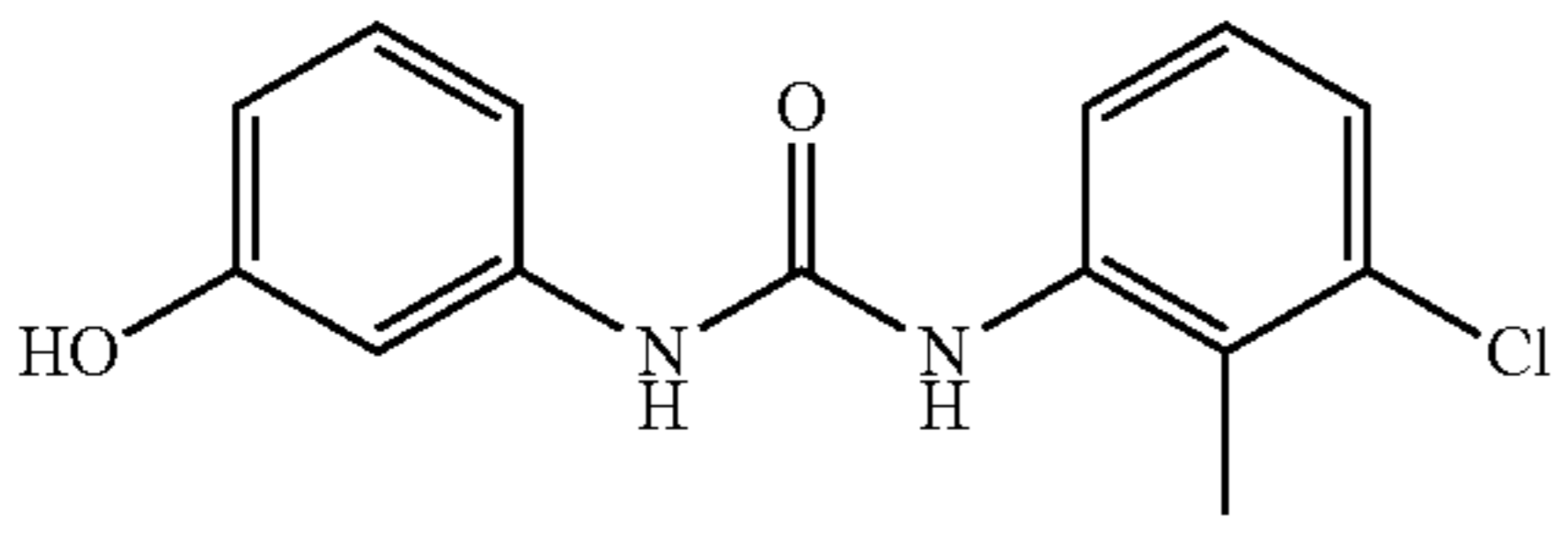
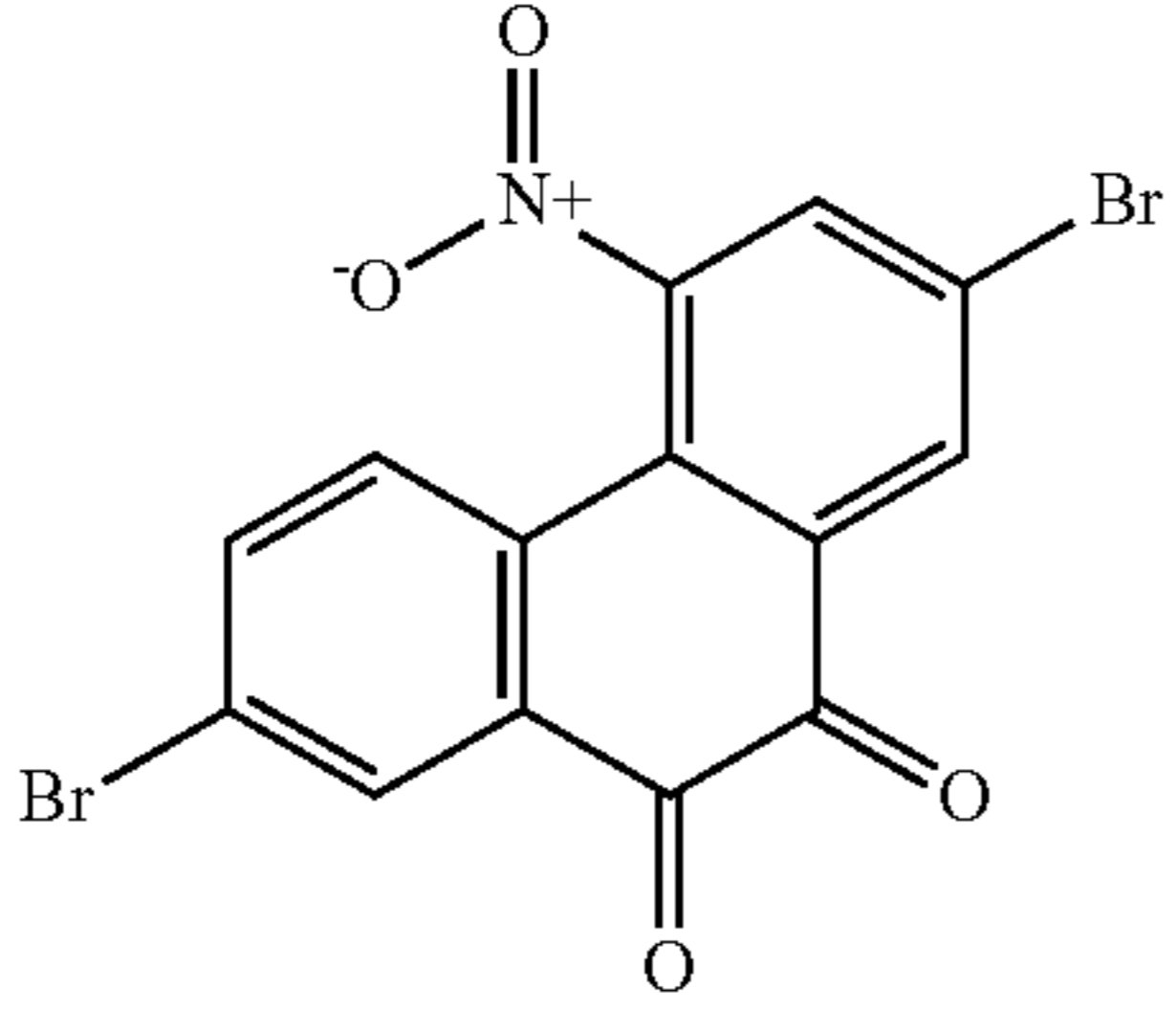
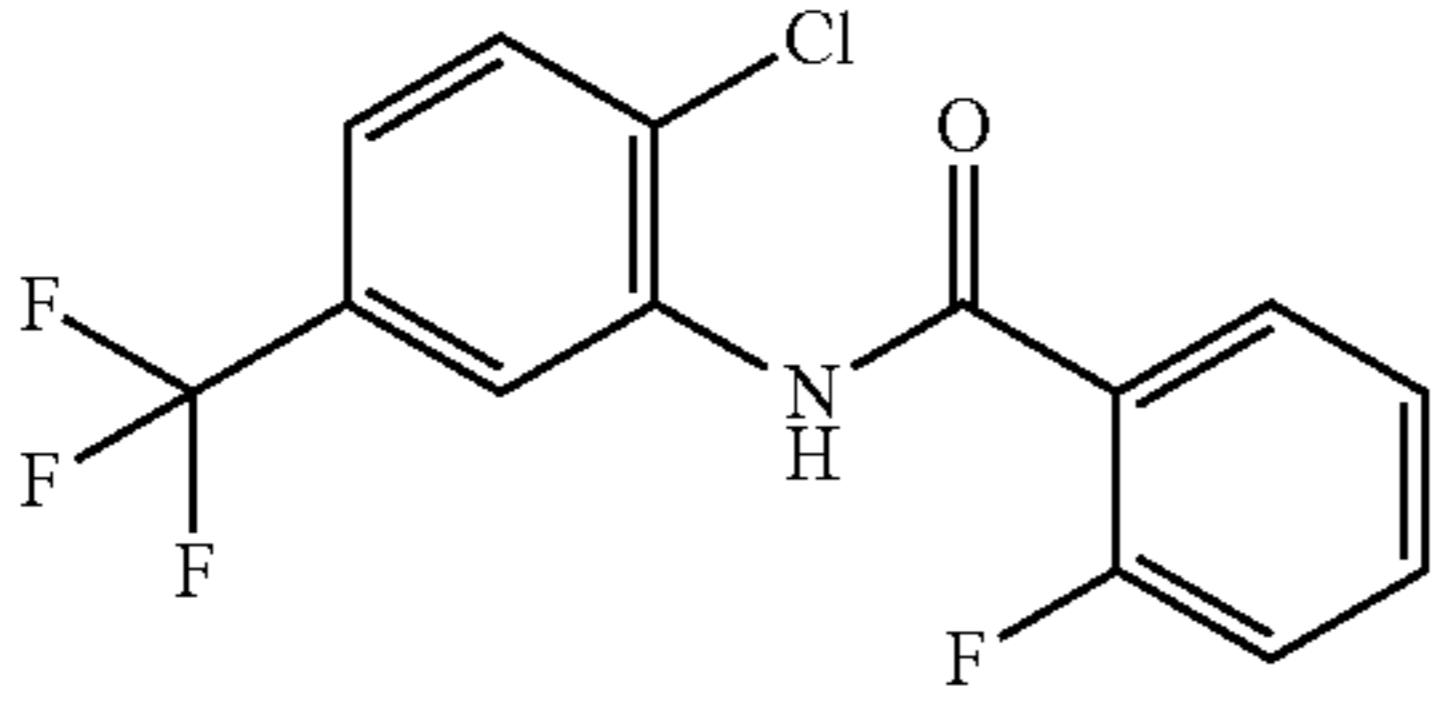
TRPV1 inhibitors.				^a K _i (μM) (or % inhibition at 30 μM)
Compound ID	Structure	LogP	MW	
10		2.62	316.70	35 ± 5%
11		3.93	337.78	3.7 ± 1.7 (61 ± 18%)
12		3.76	369.32	23 ± 12 %
13		4.17	326.78	3.7 ± 1.0 (72 ± 18%)
14		3.36	341.30	0.47 ± 0.18 (100 ± 0%)
15		4.17	326.18	0.49 ± 0.14 (99.6 ± 0.40%)

TABLE 1-continued

TRPV1 inhibitors.				
Compound ID	Structure	LogP	MW	^a K _i (μM) (or % inhibition at 30 μM)
16		3.17	276.72	0.56 ± 0.16 (100 ± 0%)
17		3.23	411.01	2.15 ± 0.72 (66 ± 11%)
18		4.48	317.67	7.0 ± 2.0 (51.8 ± 6.6%)

^aK_i values for capsaicin antagonism. For weak compounds, the % inhibition at 30 M is given. ^bCompound 5 was identified as a partial agonist. The value listed is for agonism. 35

Example 9. Binding at the Cannabinoid Receptor 2 (CB2)

The compounds were also tested for activity in the CB2 40 receptor, and showed that the binding curve for compound 15 with a K_i value of 1.39 M at CB2, while 14 and 16 showed weak binding activity with a K_i value of 15.9 μM and 12.2 μM.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 2

<210> SEQ ID NO 1

<211> LENGTH: 839

<212> TYPE: PRT

<213> ORGANISM: Homo sapiens

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Gln Lys Asp Thr Cys Pro Asp Pro Leu Asp Gly Asp Pro Asn Ser Arg
20 25 30

Pro Pro Pro Ala Lys Pro Gln Leu Ser Thr Ala Lys Ser Arg Thr Arg
35 40 45

Leu Phe Gly Lys Gly Asp Ser Glu Glu Ala Phe Pro Val Asp Cys Pro
50 55 60

-continued

His Glu Glu Gly Glu Leu Asp Ser Cys Pro Thr Ile Thr Val Ser Pro
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 Val Ile Thr Ile Gln Arg Pro Gly Asp Gly Pro Thr Gly Ala Arg Leu
 85 90 95
 Leu Ser Gln Asp Ser Val Ala Ala Ser Thr Glu Lys Thr Leu Arg Leu
 100 105 110
 Tyr Asp Arg Arg Ser Ile Phe Glu Ala Val Ala Gln Asn Asn Cys Gln
 115 120 125
 Asp Leu Glu Ser Leu Leu Leu Phe Leu Gln Lys Ser Lys Lys His Leu
 130 135 140
 Thr Asp Asn Glu Phe Lys Asp Pro Glu Thr Gly Lys Thr Cys Leu Leu
 145 150 155 160
 Lys Ala Met Leu Asn Leu His Asp Gly Gln Asn Thr Thr Ile Pro Leu
 165 170 175
 Leu Leu Glu Ile Ala Arg Gln Thr Asp Ser Leu Lys Glu Leu Val Asn
 180 185 190
 Ala Ser Tyr Thr Asp Ser Tyr Tyr Lys Gly Gln Thr Ala Leu His Ile
 195 200 205
 Ala Ile Glu Arg Arg Asn Met Ala Leu Val Thr Leu Leu Val Glu Asn
 210 215 220
 Gly Ala Asp Val Gln Ala Ala Ala His Gly Asp Phe Phe Lys Lys Thr
 225 230 235 240
 Lys Gly Arg Pro Gly Phe Tyr Phe Gly Glu Leu Pro Leu Ser Leu Ala
 245 250 255
 Ala Cys Thr Asn Gln Leu Gly Ile Val Lys Phe Leu Leu Gln Asn Ser
 260 265 270
 Trp Gln Thr Ala Asp Ile Ser Ala Arg Asp Ser Val Gly Asn Thr Val
 275 280 285
 Leu His Ala Leu Val Glu Val Ala Asp Asn Thr Ala Asp Asn Thr Lys
 290 295 300
 Phe Val Thr Ser Met Tyr Asn Glu Ile Leu Met Leu Gly Ala Lys Leu
 305 310 315 320
 His Pro Thr Leu Lys Leu Glu Glu Leu Thr Asn Lys Lys Gly Met Thr
 325 330 335
 Pro Leu Ala Leu Ala Ala Gly Thr Gly Lys Ile Gly Val Leu Ala Tyr
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 Ile Leu Gln Arg Glu Ile Gln Glu Pro Glu Cys Arg His Leu Ser Arg
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 Lys Phe Thr Glu Trp Ala Tyr Gly Pro Val His Ser Ser Leu Tyr Asp
 370 375 380
 Leu Ser Cys Ile Asp Thr Cys Glu Lys Asn Ser Val Leu Glu Val Ile
 385 390 395 400
 Ala Tyr Ser Ser Ser Glu Thr Pro Asn Arg His Asp Met Leu Leu Val
 405 410 415
 Glu Pro Leu Asn Arg Leu Leu Gln Asp Lys Trp Asp Arg Phe Val Lys
 420 425 430
 Arg Ile Phe Tyr Phe Asn Phe Leu Val Tyr Cys Leu Tyr Met Ile Ile
 435 440 445
 Phe Thr Met Ala Ala Tyr Tyr Arg Pro Val Asp Gly Leu Pro Pro Phe
 450 455 460
 Lys Met Glu Lys Thr Gly Asp Tyr Phe Arg Val Thr Gly Glu Ile Leu
 465 470 475 480

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Ser Val Leu Gly Gly Val Tyr Phe Phe Phe Arg Gly Ile Gln Tyr Phe
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 Leu Gln Arg Arg Pro Ser Met Lys Thr Leu Phe Val Asp Ser Tyr Ser
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 Glu Met Leu Phe Phe Leu Gln Ser Leu Phe Met Leu Ala Thr Val Val
 515 520 525
 Leu Tyr Phe Ser His Leu Lys Glu Tyr Val Ala Ser Met Val Phe Ser
 530 535 540
 Leu Ala Leu Gly Trp Thr Asn Met Leu Tyr Tyr Thr Arg Gly Phe Gln
 545 550 555 560
 Gln Met Gly Ile Tyr Ala Val Met Ile Glu Lys Met Ile Leu Arg Asp
 565 570 575
 Leu Cys Arg Phe Met Phe Val Tyr Ile Val Phe Leu Phe Gly Phe Ser
 580 585 590
 Thr Ala Val Val Thr Leu Ile Glu Asp Gly Lys Asn Asp Ser Leu Pro
 595 600 605
 Ser Glu Ser Thr Ser His Arg Trp Arg Gly Pro Ala Cys Arg Pro Pro
 610 615 620
 Asp Ser Ser Tyr Asn Ser Leu Tyr Ser Thr Cys Leu Glu Leu Phe Lys
 625 630 635 640
 Phe Thr Ile Gly Met Gly Asp Leu Glu Phe Thr Glu Asn Tyr Asp Phe
 645 650 655
 Lys Ala Val Phe Ile Ile Leu Leu Leu Ala Tyr Val Ile Leu Thr Tyr
 660 665 670
 Ile Leu Leu Leu Asn Met Leu Ile Ala Leu Met Gly Glu Thr Val Asn
 675 680 685
 Lys Ile Ala Gln Glu Ser Lys Asn Ile Trp Lys Leu Gln Arg Ala Ile
 690 695 700
 Thr Ile Leu Asp Thr Glu Lys Ser Phe Leu Lys Cys Met Arg Lys Ala
 705 710 715 720
 Phe Arg Ser Gly Lys Leu Leu Gln Val Gly Tyr Thr Pro Asp Gly Lys
 725 730 735
 Asp Asp Tyr Arg Trp Cys Phe Arg Val Asp Glu Val Asn Trp Thr Thr
 740 745 750
 Trp Asn Thr Asn Val Gly Ile Ile Asn Glu Asp Pro Gly Asn Cys Glu
 755 760 765
 Gly Val Lys Arg Thr Leu Ser Phe Ser Leu Arg Ser Ser Arg Val Ser
 770 775 780
 Gly Arg His Trp Lys Asn Phe Ala Leu Val Pro Leu Leu Arg Glu Ala
 785 790 795 800
 Ser Ala Arg Asp Arg Gln Ser Ala Gln Pro Glu Glu Val Tyr Leu Arg
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 Gln Phe Ser Gly Ser Leu Lys Pro Glu Asp Ala Glu Val Phe Lys Ser
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 Pro Ala Ala Ser Gly Glu Lys
 835

<210> SEQ ID NO 2

<211> LENGTH: 838

<212> TYPE: PRT

<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 2

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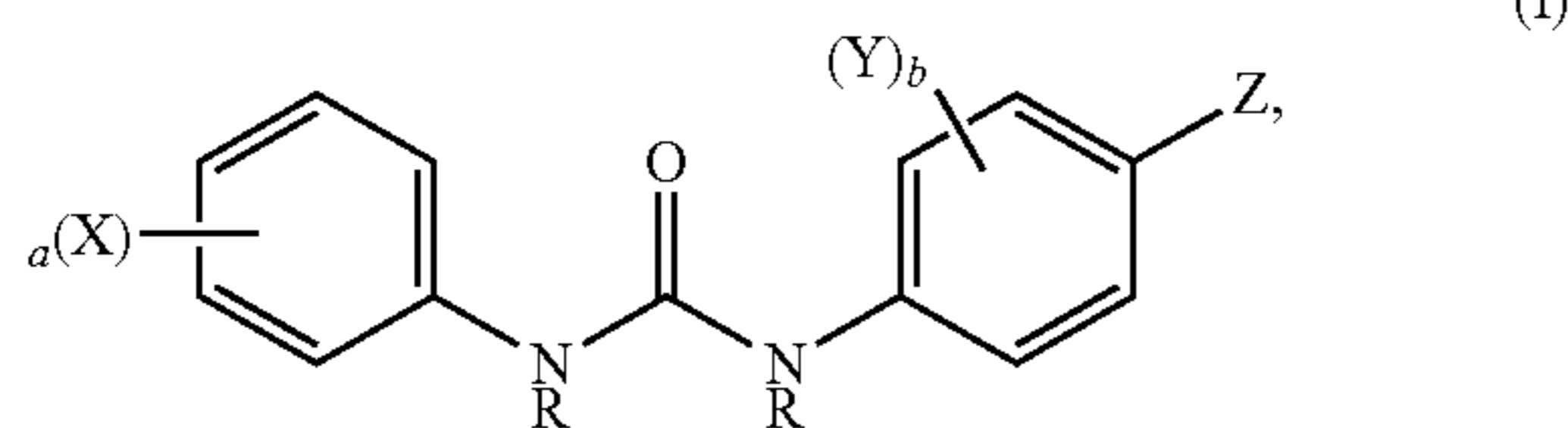
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Gln Glu Asn Ser Cys Leu Asp Pro Pro Asp Arg Asp Pro Asn Cys Lys
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 Pro Pro Pro Val Lys Pro His Ile Phe Thr Thr Arg Ser Arg Thr Arg
 35 40 45
 Leu Phe Gly Lys Gly Asp Ser Glu Glu Ala Ser Pro Leu Asp Cys Pro
 50 55 60
 Tyr Glu Glu Gly Gly Leu Ala Ser Cys Pro Ile Ile Thr Val Ser Ser
 65 70 75 80
 Val Leu Thr Ile Gln Arg Pro Gly Asp Gly Pro Ala Ser Val Arg Pro
 85 90 95
 Ser Ser Gln Asp Ser Val Ser Ala Gly Glu Lys Pro Pro Arg Leu Tyr
 100 105 110
 Asp Arg Arg Ser Ile Phe Asp Ala Val Ala Gln Ser Asn Cys Gln Glu
 115 120 125
 Leu Glu Ser Leu Leu Pro Phe Leu Gln Arg Ser Lys Lys Arg Leu Thr
 130 135 140
 Asp Ser Glu Phe Lys Asp Pro Glu Thr Gly Lys Thr Cys Leu Leu Lys
 145 150 155 160
 Ala Met Leu Asn Leu His Asn Gly Gln Asn Asp Thr Ile Ala Leu Leu
 165 170 175
 Leu Asp Val Ala Arg Lys Thr Asp Ser Leu Lys Gln Phe Val Asn Ala
 180 185 190
 Ser Tyr Thr Asp Ser Tyr Tyr Lys Gly Gln Thr Ala Leu His Ile Ala
 195 200 205
 Ile Glu Arg Arg Asn Met Thr Leu Val Thr Leu Leu Val Glu Asn Gly
 210 215 220
 Ala Asp Val Gln Ala Ala Ala Asn Gly Asp Phe Phe Lys Lys Thr Lys
 225 230 235 240
 Gly Arg Pro Gly Phe Tyr Phe Gly Glu Leu Pro Leu Ser Leu Ala Ala
 245 250 255
 Cys Thr Asn Gln Leu Ala Ile Val Lys Phe Leu Leu Gln Asn Ser Trp
 260 265 270
 Gln Pro Ala Asp Ile Ser Ala Arg Asp Ser Val Gly Asn Thr Val Leu
 275 280 285
 His Ala Leu Val Glu Val Ala Asp Asn Thr Val Asp Asn Thr Lys Phe
 290 295 300
 Val Thr Ser Met Tyr Asn Glu Ile Leu Ile Leu Gly Ala Lys Leu His
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 Pro Thr Leu Lys Leu Glu Glu Ile Thr Asn Arg Lys Gly Leu Thr Pro
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 Leu Ala Leu Ala Ala Ser Ser Gly Lys Ile Gly Val Leu Ala Tyr Ile
 340 345 350
 Leu Gln Arg Glu Ile His Glu Pro Glu Cys Arg His Leu Ser Arg Lys
 355 360 365
 Phe Thr Glu Trp Ala Tyr Gly Pro Val His Ser Ser Leu Tyr Asp Leu
 370 375 380
 Ser Cys Ile Asp Thr Cys Glu Lys Asn Ser Val Leu Glu Val Ile Ala
 385 390 395 400
 Tyr Ser Ser Ser Glu Thr Pro Asn Arg His Asp Met Leu Leu Val Glu
 405 410 415
 Pro Leu Asn Arg Leu Leu Gln Asp Lys Trp Asp Arg Phe Val Lys Arg
 420 425 430

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What is claimed is:

1. A method of treating pain associated with transient receptor potential vanilloid type 1 (TRPV1) in a subject in need thereof, comprising administering to the subject an effective amount of a compound represented by Formula (I):



wherein:

X is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Y is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Z is halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R is independently in each instance H, -OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R' is independently in each instance H, -OH, (C₁-C₆)alkyl, (C₁-C₆) perfluoroalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-

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(C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

a is an integer of 0 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

2. The method of claim 1, wherein Z is N(R')₂ or NO₂ and a is an integer of 1 to 5; and b is an integer of 0 to 4.

3. The method of claim 1, wherein:

X is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl;

Y is independently in each instance halogen, C₁-C₆ alkyl;

Z is N(R')₂ or NO₂;

R is independently in each instance H or C₁-C₆ alkyl;

R' is independently in each instance H, C₁-C₆ alkyl, or C₁-C₆ perfluoroalkyl;

a is an integer of 1 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

4. The method of claim 1, wherein a and b are each independently an integer of 1 to 3.

5. The method of claim 1, wherein a and b are one.

6. The method of claim 1, wherein X is fluoro, C₁-C₆ alkyl or C₁-C₆ perfluoroalkyl and a is 1.

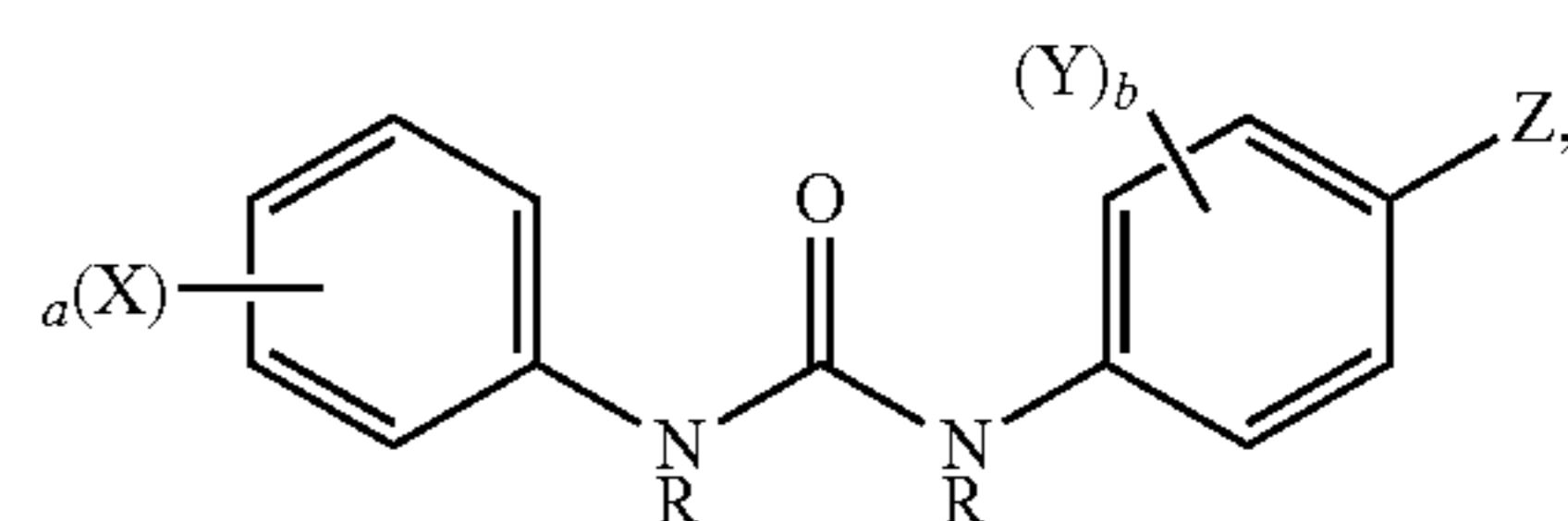
7. The method of claim 1, wherein Y is a C₁-C₆ alkyl and b is 1.

8. The method of claim 1, wherein R is H.

9. The method of claim 1, wherein Z is NO₂.

10. The method of claim 1, wherein the pain associated with TRPV1 is selected from the group consisting of osteoarthritis, neuropathic pain, migraine, inflammatory bowel disease, and bone cancer pain.

11. A method of inhibiting the activity of TRPV1 comprising contacting TRPV1 with a compound represented by Formula (I):



wherein:

X is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC(O)-C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -NH₂, -NH(C₁-C₆)alkyl, -N[(C₁-C₆)alkyl]₂, -CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Y is independently in each instance halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)-C₁-C₆ alkyl, NHC

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(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

Z is halogen, OH, amino, COOH, CONH₂, SO₃H, PO₃H₂, CN, SH, N(R')₂, NO₂, CF₃C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆)perfluoroalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

R' is independently in each instance H, —OH, (C₁-C₆)alkyl, (C₁-C₆)perfluoroalkyl, (C₁-C₆)alkoxy, (C₁-C₆)haloalkoxy, (C₁-C₆)haloalkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, —NH₂, —NH(C₁-C₆)alkyl, —N[(C₁-C₆)alkyl]₂, —CN, (C₃-C₈)heteroaryl, (C₃-C₈)heterocycloalkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)aryl, (C₃-

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C₈)heterocycloalkyl-(C₁-C₆)alkylene-, (C₃-C₈)heteroaryl-(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkylene-, (C₃-C₈)aryl(C₁-C₆)alkenylene-, or (C₁-C₆)alkyl-(C₃-C₈)arylene;

a is an integer of 0 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

12. The method of claim 11, wherein Z is N(R')₂ or NO₂ and a is an integer of 1 to 5; and b is an integer of 0 to 4.

13. The method of claim 11, wherein:

X is independently in each instance halogen, C₁-C₆ alkyl, C₁-C₆ perfluoroalkyl, NHC(O)—C₁-C₆ alkyl, NHC(O)—C₁-C₆ perfluoroalkyl;

Y is independently in each instance halogen, C₁-C₆ alkyl; Z is N(R')₂ or NO₂;

R is independently in each instance H or C₁-C₆ alkyl;

R' is independently in each instance H, C₁-C₆ alkyl, or C₁-C₆ perfluoroalkyl;

a is an integer of 1 to 5; and

b is an integer of 0 to 4,

wherein the alkyl moieties are optionally substituted by one or more halogen, or a pharmaceutically acceptable salt or solvate thereof.

14. The method of claim 11, wherein a and b are each independently an integer of 1 to 3.

15. The method of claim 11, wherein a and b are one.

16. The method of claim 11, wherein X is fluoro, C₁-C₆ alkyl or C₁-C₆ perfluoroalkyl and a is 1.

17. The method of claim 11, wherein Y is a C₁-C₆ alkyl and b is 1.

18. The method of claim 11, wherein R is H.

19. The method of claim 11, wherein Z is NO₂.

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